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THE INCIDENCE OF ABNORMAL BLOOD LEVELS OF LEAD IN A METROPOLITAN PEDIATRIC CLINIC

WITH OBSERVATION ON THE VALUE OF COPROPORPHYRINURIA AS A SCREENING TEST

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FROM Jan. 1, 1931, to Jan. 1, 1955, 462 children were admitted to Baltimore hospitals with lead encephalopathy or other manifestations of lead intoxication.[1-3] The majority of these children lived in the congested, low-income areas of Baltimore. Lead paint had been used to paint the interior of the houses for many years and in many cases the paint was flaking and scaling, so that the children had opportunity to eat the flakes of paint or chew on the painted surfaces.

This large number of cases suggested that there might be a high incidence of lead intoxication among children living in the same areas as those reported, and yet not showing significant or recognized symptoms of lead intoxication.

Since many industrial firms[4, 5] have used qualitative urinary coproporphyrin III testing as a method of screening their workers for exposure to dangerous amounts of lead, it was our opinion that this test might lend itself to screening large numbers of children for evidence of lead intoxication, and, hence, aid in determining whether the preceding premise was correct.

METHODS AND MATERIALS

The Well-Baby Clinic of the Baltimore City Department of Health and the Pediatric Outpatient Department at the University of Maryland Hospital serving the children of a congested, low-income area in Baltimore provided the source of patients. The children ranged in age from 7 to 60 months, 90 per cent of whom were Negroes. Children of this age seen in the clinic from Aug. 1, 1953, to Sept. 1, 1954, were included.

A freshly voided specimen of urine was obtained from each patient at the time of the clinic visit. A plastic collection diaper* was used for subjects not toilet trained. The urine was then examined for coproporphyrin III, using the deLangen-ten Berg test[6]

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*Tomac urine specimen diaper, American Hospital Supply Corporation, Evanston, Ill.

modified by McCord.[7] All subjects with a positive coproporphyrin of 2 plus (reddish fluorescence) or more and alternate children with a negative coproporphyrin had the following additional studies: blood lead determination (dithizone method),[8] hemoglobin, erythrocyte count, smear for stippling, roentgenogram of long bones, a complete history, and a careful physical examination.

Positive coproporphyrinuria of 2 plus or more was present in 197 children. In addition to the coproporphyrinuria, 124 of these children gave a history of pica for paint or plaster. Areas of increased density at the epiphyseal ends of the long bones, compatible with heavy metal deposition, were found in fifty-one children. A hemoglobin value of less than 10 grams was present in sixty-six children, and

TABLE I. FINDINGS AND SYMPTOMS IN CHILDREN WITH POSITIVE COPROPORPHYRINURIA

BLOOD LEAD LEVEL (MG. %)	POSITIVE COPRO-PORPHYRIN (NO.)	PICA (NO.)	DENSE EPIPHYSEAL LINES (NO.)	Hb. 10 GM. (NO.)	STIPPLING ERYTHRO-CYTES (NO.)	GASTRO-INTESTINAL SYMPTOMS (NO.)	C.N.S. SYMPTOMS (NO.)
0.019 or less	1	0	0	0	0	0	0
0.020-0.029	21	9	2	10	4	11	2
0.030-0.039	36	17	0	11	4	13	1
0.040-0.049	43	23	3	9	2	12	2
0.050-0.059	42	27	18	12	5	7	3
0.060-0.069	28	25	10	9	7	11	4
0.070-0.079	13	10	8	5	5	3	1
0.080-0.089	6	6	4	4	1	3	3
0.090-0.099	1	1	1	1	0	1	1
0.10 or more	6	6	5	5	1	3	2
Total	197	124	51	66	29	64	19

TABLE II. FINDINGS AND SYMPTOMS IN CHILDREN WITH NEGATIVE COPROPORPHYRINURIA

BLOOD LEAD LEVEL (MG. %)	NEGATIVE COPRO-PORPHYRIN (NO.)	PICA (NO.)	DENSE EPIPHYSEAL LINES (X-RAY) (NO.)	Hb. (GM.) (NO.)	STIPPLING ERYTHRO-CYTES (NO.)	GASTRO-INTESTINAL SYMPTOMS (NO.)	C.N.S. SYMPTOMS (NO.)
0.019 or less	–	–	–	–	–	–	–
0.020-0.029	12	6	0	6	5	3	2
0.030-0.039	27	10	0	8	2	5	3
0.040-0.049	45	17	4	24	5	7	2
0.050-0.059	20	5	3	9	3	3	1
0.060-0.069	18	11	6	9	4	3	0
0.070-0.079	6	3	4	5	1	2	0
0.080-0.089	4	3	3	2	0	1	0
0.090-0.099	–	–	–	–	–	–	–
0.10 or more	4	4	4	2	0	2	0
Total	136	59	24	65	20	26	8

RESULTS AND OBSERVATIONS

There were 604 freshly voided urine specimens from 604 children, aged 7 to 60 months, examined for coproporphyrin III by the previously described method.

stippled red blood cells in twenty-nine. Sixty-four children had gastrointestinal symptoms, such as vomiting, abdominal pain, and constipation, and nineteen had central nervous system symptoms as irritability, lethargy, and

convulsions. There were ninety-six children in this group with a blood lead value of 0.05 mg. per cent or higher. (Table I.)

There were 136 children in the negative coproporphyrinuria group. Fifty-nine of these children gave a history of pica for paint or plaster. There were areas of increased density at the epiphyseal ends of the long bones in twenty-four children. Sixty-five children had a hemoglobin of less than 10 grams, and twenty had stippling of the red blood cells. Gastrointestinal symptoms were present in twenty-six children, and central nervous system symptoms in eight. There were fifty-two children in this group with a blood lead value of 0.05 mg. per cent or higher. (Table II.)

DISCUSSION

Lead intoxication in children, prior to manifest encephalopathic symptoms, produces vague and indefinite symptoms referable to the gastrointestinal tract and/or central nervous system. The suspicion that lead may be the cause of the symptoms can be obtained through inquiring if the child has been eating or chewing on painted surfaces. The importance in including this question in supporting the impression of lead intoxication is shown in this study where 69.6 per cent of the children with a blood lead of 0.05 mg. per cent or higher gave a history of pica. This one finding gave higher correlation with the blood lead than any other single test or symptom.

A roentgenogram of the long bones may be of help in confirming the impression of lead poisoning,[9] particularly in children whose blood lead is 0.06 mg. per cent or higher. In this study 51.1 per cent of the children with a blood lead in this range had changes in the long bones compatible with heavy metal deposition. However, the percentage of radiographic changes in the children with a blood lead of 0.05 to 0.059 mg. per cent was only 32.2 per cent. The use of the radiogram as a diagnostic tool in the diagnosis of lead poisoning is restricted to children under 10 years of age,[10] as the lines of increased density appear only during the rapid growing period of bone.

Anemia can be produced by lead poisoning either through destruction of blood or suppression of the hematopoietic system. In this study 38.8 per cent of the children with a blood lead less than 0.05 mg. per cent had a hemoglobin of less than 10 grams, whereas 44 per cent of the children with a blood lead higher than 0.05 mg. per cent had a hemoglobin of less than 10 grams. It is clear that the presence of anemia alone can hardly be interpreted as being of diagnostic value in lead poisoning.

Kehoe[11] and others[12] have shown that the occurrence of basophilic material in the erythrocytes has no diagnostic significance. The occurrence of basophilic stippling in 18 per cent of the children with a blood lead of 0.05 mg. per cent or higher and in 14 per cent of those with a blood lead of 0.049 mg. per cent or less confirms their observation.

Coproporphyrinuria, though found in many conditions, is considered to be an important physiologic response to lead poisoning.[13] The increase in coproporphyrin III is attributed to a disturbance in hemoglobin breakdown and synthesis, lead probably interfering with the introduction of iron into the hemoglobin molecule, with resultant increased coproporphyrin excretion.[14] That the qualitative urinary

test for the presence of coproporphyrin III does not provide an indication of blood lead content has been reported.[15] There were 38.2 per cent of children in this study with abnormal (0.05 mg. per cent and higher) blood lead values and yet with negative coproporphyrinuria. This incidence is high and indicates that the use of the qualitative test alone for screening will result in many children with abnormal amounts of lead in blood escaping detection. (Table III.)

0.05 and 0.08 mg. per cent were admitted to the University Hospital with lead encephalopathy. This experience emphasizes the need to consider any child with an abnormal blood lead as having potentially dangerous lead intoxication.

The mean blood lead in this study was found to be 0.043 mg. per cent (Fig. 1). The blood lead level of a group of Baltimore children selected at random and reported by Kaplan and McDonald[17] in 1938 was 0.03 mg.

TABLE III. PER CENT OF FINDINGS AND SYMPTOMS RELATED TO COPROPORPHYRINURIA

	CHILDREN WITH POSITIVE COPROPORPHYRINURIA		CHILDREN WITH NEGATIVE COPROPORPHYRINURIA		TOTAL	
	NO. (197)	% (100)	NO. (136)	% (100)	NO. (333)	% (100)
Pica	124	62.9	59	43.3	183	54.9
X-ray changes	51	25.9	24	17.6	75	22.5
Hb. 10 grams	66	33.5	65	47.7	121	36.3
Stippling	29	14.7	20	15.5	49	14.7
Abdominal symptoms	64	32.4	26	19.1	90	27.0
C.N.S. symptoms	19	9.1	8	5.9	27	8.1
Blood lead 0.05 mg. % or higher	96	48.7	52	38.2	148	44.4

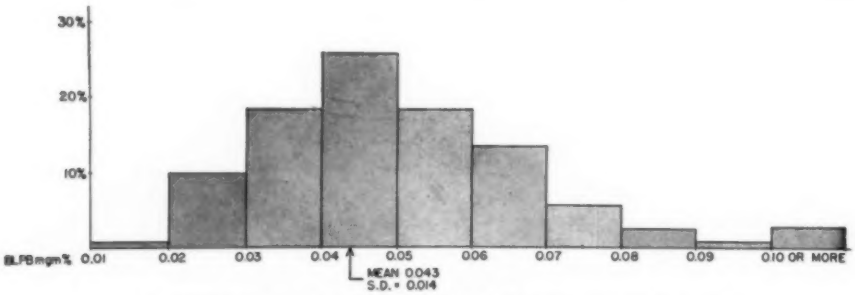

Fig. 1.—Distribution and mean value of blood lead among 333 children.

There has been reasonable correlation established between blood lead value and the diagnosis of lead intoxication.[16] In this study a number of children with abnormal blood lead values were asymptomatic. However, while the study was in progress, eight of the children, previously asymptomatic, with blood lead values between

per cent. It is not possible to compare these two studies, as the present study was biased, since the subjects were selected from a low-income group living in the same geographic area. The 1938 study was done with children admitted to the Sydenham (contagious disease) Hospital and represented children from various socioeconomic and

geographic areas. The present study, however, suggests that the blood lead value of 0.05 mg. per cent is probably the upper limit of normal, since at this level there was an increase in other findings compatible with the diagnosis of lead intoxication.

The distribution of blood lead according to age (Table IV) shows an absence of abnormal values among infants from 7 to 10 months of age. This is an expected finding since the infant at this age has a limited cruising range and is likely to eat toxic particles found only in his immediate vicinity.

TABLE IV. DISTRIBUTION OF CHILDREN ACCORDING TO BLOOD LEAD LEVEL AND AGE

BLOOD LEAD LEVEL (MG. %)	7-10 MO.	10-18 MO.	18-24 MO.	24-30 MO.	30-36 MO.	36-42 MO.	42-48 MO.	48-60 MO.
0.019 or less	0	1	0	0	0	0	0	0
0.020-0.029	8	9	4	2	2	3	2	3
0.030-0.039	8	14	9	11	4	3	6	7
0.040-0.049	5	20	10	17	10	8	3	14
0.050-0.059	0	16	6	16	7	3	3	11
0.060-0.069	0	5	11	7	10	4	4	4
0.070-0.079	0	2	7	1	3	5	1	0
0.080-0.089	0	2	1	1	2	1	1	2
0.090-0.099	0	0	1	0	0	0	0	0
0.10 or higher	0	0	1	4	3	1	1	0

The findings of abnormal blood lead values in 44.4 per cent of 333 children studied complement the high incidence of lead encephalopathy previously reported in Baltimore. This finding also suggests that there might well be a high incidence of unrecognized lead intoxication in other metropolitan areas where a number of children live in old, congested, low-income housing areas. The occurrence of lead intoxication to this extent demands immediate and effective application of prophylactic measures.

SUMMARY

1. Six hundred four children, aged 7 to 60 months, were examined for qualitative urinary coproporphyrin III.

2. Positive coproporphyrin of 2 plus or more was found in 197.

3. Blood lead determinations, x-ray of long bones, hematologic examinations, and a complete history and a careful physical examination were done on all those with positive coproporphyrinuria and in 136 subjects with negative coproporphyrinuria.

4. The mean blood lead for the two groups was 0.043 mg. per cent.

5. The upper limit of normal blood lead seems to be 0.05 mg. per cent as at this value and above there was an increase in symptoms and findings ascribed to lead intoxication, though serious lead intoxication can in some individuals occur at lower values.

6. There was no significant difference of blood lead or other findings of lead intoxication in the patients with or without coproporphyrinuria.

7. Abnormal blood lead values were found in 44.4 per cent of the 333 children studied.

8. A history of pica was noted in 69.6 per cent of the children with a blood lead of 0.05 mg. per cent or higher. This one finding gave higher correlation with blood lead than any other single test or symptom.

9. These findings suggest that children living in other metropolitan areas where lead paint has been used in the

houses for many years should be investigated for evidences of lead poisoning.

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MULTIPLE SKELETAL LESIONS IN YOUNG CHILDREN DUE TO TRAUMA

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IN 1946 Caffey[1] described six patients with subdural hematoma who exhibited twenty-three fractures and four contusions of the long bones. In not a single case was a history of trauma obtainable. Since then he has called attention repeatedly, in conferences and teaching sessions, to the frequency with which trauma produces skeletal changes in infants and young children. During recent years a number of reports have appeared which confirm Caffey's observation.[2-4]

Despite their frequency, traumatic bone lesions in early childhood are often missed. There are several reasons for this: a history of a traumatic episode is often not obtained. The symptoms, when present, are generally mild and easily overlooked or minimized. The roentgen changes may not appear for several days after the injury; moreover, they are unlike the changes characteristic of trauma during later childhood and adult life. And, finally, the roentgen changes are often multiple and are consequently confused with some deep-seated bone disease.

ETIOLOGY

Babies frequently fall or are dropped. The traumatic episode may be forgotten or suppressed. If the immediate symptoms are not severe, as is usually the case, the episode may be considered too trivial to mention. Sometimes one parent is afraid to tell the other about an injury. So, too, a sitter, relative, or nurse may be reluctant to report to the parents that a mishap has taken place, since she fears that she may be accused of negligence. A baby may be injured by an older sibling in the course of rough play as in Case 1 described below.

Woolley and Evans[4] emphasize that the injury is often deliberately inflicted by a parent or custodian. Parental indifference, ignorance, preoccupation with other duties, alcoholism, psychoneurosis or psychosis, relegation of control to irresponsible children or adults, and improper physical equipment or environment contribute to the frequency with which skeletal injury takes place.

Bone trauma is sometimes produced by the baby's legs getting caught in the rungs of the crib. Seizing the child roughly by the hand may cause lesions about the shoulder.

Injury not infrequently takes place during the birth process, particularly during breech delivery. The roentgen changes in newborn infants have been described by Snedecor and associates[5] and by Snedecor and Wilson.[6]

The most frequent clinical manifestations are pain, irritability, tenderness, and restricted motion. These signs are generally mild and easily overlooked. Skin bruises are occasionally seen, but the large skin ecchymoses

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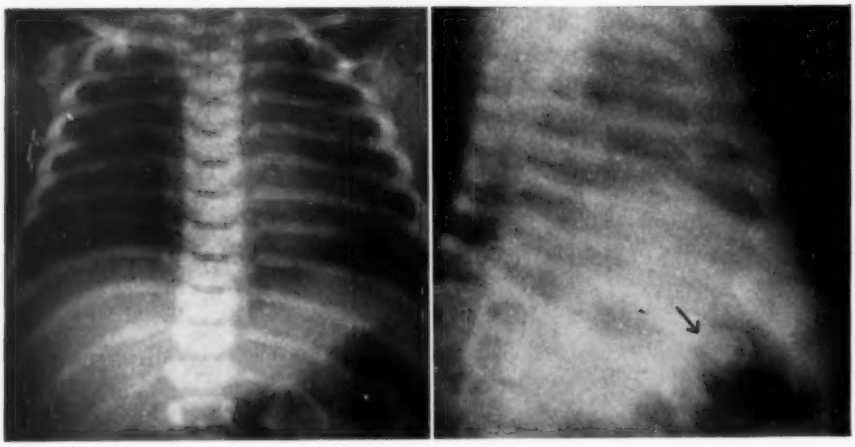
A. *B.*



C. *D.*

Fig. 1.—A boy, 4½ months of age. Injury by an older sibling during rough play. *A*, Right humerus. Subperiosteal ossification over upper portion of the bone with irregular new bone formation. *B*, Legs. Subperiosteal ossification over lower portions of the tibias, more marked on the right. The periosteal cloaking extends beyond the distal ends of the tibias. *C*, Chest showing fractures of the fifth, sixth, seventh, eleventh, and twelfth ribs on the right and the twelfth rib on the left. *D*, Halolike calcium ring about the end of the left ninth rib. Case 1.

seen at a later age in the region of fractures are not ordinarily found except when gross breaks occur. Some children have no symptoms and the bone changes are found accidentally when roentgenograms are taken for other reasons. The serum calcium and phosphorus are normal.

ROENTGEN CHANGES

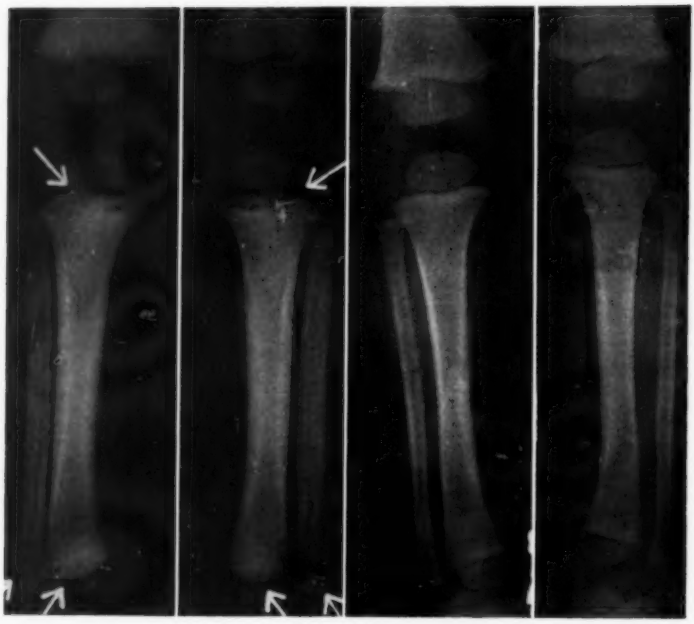
The roentgen changes in the bones seen after injuries in young children are subperiosteal ossification, avulsion of parts of the provisional zone of calcification, metaphyseal fractures, impacted fractures, gross fractures, and epiphyseal displacements.

The most frequent change seen in the roentgenograms is cortical thickening, the result of periosteal separation and subperiosteal ossification. An example is shown in Fig. 1, *A* and *B*. The periosteum in young children is easily stripped from the bone and highly vascular. After an injury no changes are seen in the roentgenograms immediately, unless there is concomitant fracture. Approximately seven to ten days later a new layer of cortical bone becomes visible. The involved bone is then cloaked by a new layer of subperiosteal bone. The extent of cloaking is generally widest at the end of the affected bone and often extends beyond the epiphyseal line, as shown in Fig. 1, *B*, where a part of the provisional zone of calcification has been torn away.

Ordinarily the new bone is limited to the subperiosteal space as indicated by the sharp straight outer margin. Sometimes the periosteum is torn and thrown into folds which produce irregular masses of new bone (Fig. 1, *A*).

A. *B.* *C.*

Fig. 2.—Multiple metaphyseal fractures in a boy 3 months of age. No history of trauma. *A*, Fracture of the left radius. *B*, Right leg. Chip fracture of the anterior margin of lower tibial metaphysis. *C*, Left leg. Chip fractures of internal condyle of the femur, the proximal and distal ends of the left tibia. Subperiosteal ossification, lower end of tibia.



A. *B.*

Fig. 3.—Multiple traumatic bone lesions in a boy 8 months of age. *A*, Fractures through the metaphyses at the distal ends of the tibias and fibulas and proximal ends of the tibias. Cortical thickening over the tibias and fibulas. Old healed fracture through the distal metaphysis of the right femur. *B*, Eight months later. Complete healing.

Fig. 4.—Impacted fracture of the femur in an infant 2 months of age. Cortical thickening (subperiosteal ossification), right femur.

"Traumatic periostitis" in young children has been described by Barmeyer and co-workers.[7] They observed subperiosteal ossification along the shafts of the femur and tibia following traumatic episodes of various sorts.

Metaphyseal fractures occur frequently after trauma in infants and young children. They are generally multiple. The patient whose films are illustrated in Fig. 2 was a 3-month-old boy in whom it was not possible to elicit a history of trauma. The infant was seen because of tenderness, swelling, and immobility of the left leg. Roentgen examination revealed chip fractures of the internal condyle of the left femur, the proximal end of the left tibia, the distal end of the left tibia, the distal anterior edge of the right tibial metaphysis, as well as a transverse fracture of the left radius with displacement. Healing took place promptly. When last seen at 4 years of age the child was well.

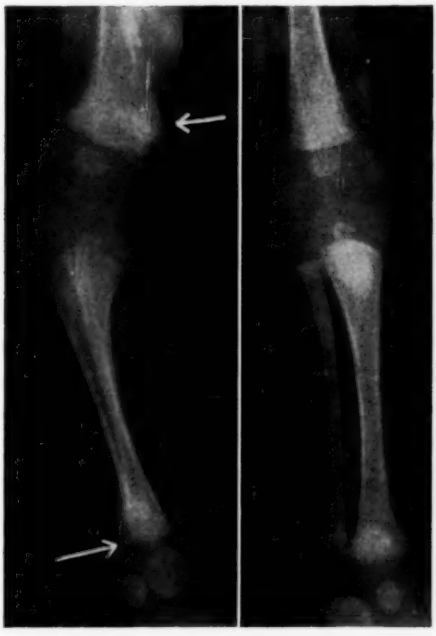


Fig. 5.

Fig. 6.

Fig. 5.—Impacted fracture of the femur in a young infant. New bone formation about the lower end of the right tibia.

Fig. 6.—Epiphyseal displacement of the proximal center of the left tibia. A thin, transverse, calcified streak is visible between the center and the bone probably due to fracture through the provisional zone of calcification.

A second example is illustrated in Fig. 3. The child, an 8-month-old boy, whose father was a chronic alcoholic, shows (Fig. 3, *A*) fractures through the metaphyses at the distal ends of tibias and fibulas and the proximal ends of the tibias, thickened cortices

over the shafts of the tibias and fibulas, and an old healed fracture through the metaphysis at the lower end of the right femur. Films taken eight months later (Fig. 3, *B*) show complete healing and normal bony texture.

It is important to remember that fractures are the only changes which are visible immediately after the injury.

Impacted Fractures.—Examples of impacted fractures are shown in Figs. 4 and 5. In the case illustrated in Fig. 4, an infant 2 months of age, there is an impacted fracture at the distal end of the left femur, with outward angulation of the lower fragment and the formation of new cortical bone. The cortical walls are thickened (subperiosteal ossification) over the right femur.

Fig. 5 illustrates an impacted fracture at the lower end of the right femur in another young infant, with outward angulation of the lower fragment and cortical thickening.

Traumatic dislocations of the epiphyseal centers are rare. When the center has been calcified, it can be seen to be out of alignment with the bony shaft. In the example shown in Fig. 6 a thin, transverse line is visible between the displaced center at the proximal end of the left tibia and the bony shaft. A thin layer of the provisional zone of calcification has been torn from the tibia along with the displaced center. This is actually a fracture through the terminal limit of the provisional zone of calcification.

ILLUSTRATIVE CASES

CASE 1.—P. C., a 4½-month-old boy of Italian parentage, was referred to the hospital because of a painful, swollen right shoulder.

During the two months preceding admission the child had been eating poorly, he screamed when he was handled, and he moved his right arm less than his left. About a week before entry a firm mass, about 1 cm. in diameter, was discovered on the left anterior wall of the thorax. The right shoulder was swollen and painful on passive motion. Fever and redness were absent. At 1 month the baby fell off a table but did not seem to be harmed by it. At 3 months scleral hemorrhages were observed. The child bruised easily.

The birth had been normal. The baby received an evaporated milk, sugar, and water mixture, and supplements of vitamin C and D. One older sibling, a boy 19 months of age was well.

On examination, the baby was thin, pale, irritable, and looked chronically ill. He could move both arms but preferred use of the left arm. The right shoulder was swollen and tender. The skin was not red or discolored. A firm mass about 1 cm. in diameter could be felt on the left anterior chest wall in the region of the seventh rib. It was attached to the rib and was not tender. The overlying skin was normal. Numerous diagnoses, among them malignancy, metabolic disturbance, and leukemia, were considered.

Roentgenograms revealed widespread bone changes (Fig. 1). The upper half of the right humerus showed cortical thickening (periosteal separation, Fig. 1, *A*). Irregular bony masses were visible outside the periosteum. Similar but less extensive changes were present over the left humerus.

Subperiosteal ossification was visible over the lower portions of both tibias (Fig. 1, *B*). The subperiosteal cloaking extended around the ends of the bones.

The right, fifth, sixth, seventh, eleventh, and twelfth ribs and the left twelfth rib were fractured (Fig. 1, *C*). The anterior end of the ninth left rib was surrounded by a bony halo (Fig. 1, *D*). The halo was about 3 mm. in thickness and was separated from the rib end by about 6 mm.

Films taken seven weeks later showed healing of the rib fractures

and advanced resolution of the lesions about the humeri and tibias. The halo about the end of the ninth rib had disappeared.

Aside from the fall at 1 month, careful questioning at first failed to elicit any history of a traumatic episode. It was finally brought out that the 19-month-old brother frequently indulged in rough play with his younger sibling. A favorite game was to sit on his little brother's chest.

A. *B.* *C.*

Fig. 7.—Arthrogryposis in a boy 25 days of age. *A*, Irregular fraying of the upper end of the left humerus. *B*, New bone formation over the distal end of the right femur. Chip fracture at the lower inner edge of the metaphysis of the right tibia. *C*, Irregular fraying and fracture, proximal end of the left tibia. Case 2.

Case 2.—A. U., a boy, was born by cesarean section two weeks before the expected date of delivery, weighing 1.77 kilograms. The infant showed the classic features of generalized arthrogryposis. In addition there were hemivertebra, sacral spina bifida, and bilateral clubfoot (equinovarus). The infant died at 6 weeks of age.

The roentgenograms taken on the twenty-fifth day of life are shown in Fig. 7. The proximal end of the left humerus was irregularly frayed. The distal end of the right femur was surrounded by an irregular mass of new cortical bone. There was a small chip fracture fragment at the distal end of the right tibia (not visible in the reproduction). The proximal end of the left tibia was irregularly frayed and showed a chip fracture. Presumably bone injury took place during the manipulations incidental to the examinations by various persons. The films also show the poor development of the muscles of the legs.

CASE 3.—R. R., a girl 3½ years of age, was admitted to the hospital because of undernutrition. The child had been deserted by her mother shortly after birth and was shifted from one foster home to another. The guardian with whom she lived for the past year was said to have beaten her.

The youngster was thin, unhappy, and unresponsive. She was content to lie in bed, speaking only an occasional word. Her nose was broken and there were numerous bruises and scars. Irregularities of the bones of the forearms could be palpated.

Roentgenograms (Fig. 8) showed cortical thickening over the upper half of the left humerus. The bones of the forearms were irregular and "knobby" in outline. They were extremely dense, presumably owing to the formation of new layers of subperiosteal bone.

Roentgenograms taken two years later showed the forearm bones still irregularly outlined, but they were now osteoporotic. The reason for the osteoporosis was not clear.

A. *B.* *C.*

Fig. 8.—Multiple trauma in a neglected girl, 3½ years of age. *A*, Left humerus. Subperiosteal ossification over the upper third. *B*, The forearm bones are irregularly outlined and extremely dense except at the ends. *C*, Forearm bones two years later. The bones are still irregular in outline but are now osteoporotic.

DIFFERENTIAL DIAGNOSIS

Skeletal injuries are most frequently confused with scurvy because of the presence of ossified subperiosteal hematoma in both. In bone trauma, however, the characteristic changes of scurvy—the ground-glass osteoporosis, the cortical thinning, the dense white line, the epiphyseal ringing—are all absent. Moreover, scurvy almost never occurs during the first five months of

life, when traumatic skeletal injury is common.

Fractures and cortical thickening are frequently seen in congenital syphilis. The changes in bony texture in congenital syphilis are usually marked and involve all the long bones symmetrically; and serological examination is generally positive.

DISCUSSION

Now that rickets and bone syphilis have become rare diseases, trauma is probably the most common cause of skeletal changes in infants and young children. Most of the cases, because of the mildness of the symptoms, are probably unrecognized. Generally no treatment is necessary and healing is complete without ill effect, but occasionally the growing cartilage is injured and permanent deformity results.

The history is often unsatisfactory either because the parents intentionally suppress details of the traumatic episode or because they are unaware of it. Silverman,[3] in his excellent presentation of this subject, cautions against overwhelming those responsible for the care of the infant with feelings of guilt. A careful explanation may be necessary, emphasizing the need, sometimes, of inflicting a minor injury to protect the child from a major accident, as in the case when a child is seized by the arm to prevent a serious fall. The ease and frequency with which skeletal injury occurs in young children and its benign course may help to allay guilt reactions. In some instances it may be wise to omit explanations of the cause of the bone lesions to the parents in order to avoid precipitating a family crisis.

The occurrence of multiple bone lesions, often without a history of previous trauma, has led Astley[8] to postulate the presence of an uderlying bony defect. Such a possibility cannot be ruled out until bone biopsies have been studied, but it seems unlikely in view of the normal appearance of the unaffected bones, the smooth healing process, and the normal subsequent development of these children.

SUMMARY

1. Traumatic lesions of the bones are common in infants and young children.

2. History of a traumatic episode is often not obtained.

3. The clinical manifestations are generally mild and easily overlooked.

4. The radiographic bone lesions are subperiosteal ossification, metaphyseal fractures, avulsions, gross fractures, impacted fractures, and epiphyseal displacements.

5. The outcome is good unless the growing cartilage has been injured.

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AN APPRAISAL OF CERTAIN ACUTE PHASE REACTANTS IN A SINGLE BLOOD SAMPLE AND THEIR VALUE IN THE DIAGNOSIS OF ACUTE RHEUMATIC FEVER

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A MODERATE amount of work has been published concerning the value of certain serum or plasma acute phase reactants in the diagnosis and/or treatment of acute rheumatic fever and allied "collagen diseases."[1-16] However, I am unaware of any published data indicating the value of the acute phase reactants on the same blood sample when used as a "battery" of tests in the differential diagnosis of the above-mentioned diseases.

Most physicians are readily able to diagnose acute rheumatic fever when it occurs in its typical form. In these situations the criteria for establishing the diagnosis recommended by Jones[17] can be easily applied. It is quite likely, however, that a significant number of patients do not manifest the typical form of the disease and so the criteria of Jones would not be sufficient to establish the diagnosis. In the subtropical climate, rheumatic fever *infrequently* occurs in its typical form; in this situation the disease is more mild in its manifestations.[18] If some of the variations in the manifestations of the disease are represented as a *spectrum*, it might be stated that there is a shift to the left on the spectrum in the subtropical climates and a shift to the right in the temperate climates. Such a spectrum is illustrated in Fig. 1.

It is in those clinical situations where the physician is considering the disease as occurring to the left of the *spectrum* and where the criteria of Jones[17] are inadequate that special diagnostic aids are most helpful. It is the purpose of this paper to report the results of the performance of a battery of certain of the acute phase reactants on the *same* sample of blood from patients with various disease states, including rheumatic fever. Implications as to the value of such tests in differentiating mild rheumatic fever from other conditions will be discussed.

MATERIALS AND METHODS

Blood was collected by venepuncture from seventy-six normal infants and children and 128 infants and children with the following various disease states: acute rheumatic fever, acute respiratory disease, streptococcosis, acute glomerulonephritis, acute rheumatoid arthritis, inactive rheumatic fever, lupus erythematosus, malignancy, obesity, asthma, and allergic rhinitis. After allowing it to clot, the blood was centrifuged, and the serum was separated and stored in the frozen state until the laboratory determinations could be made. Care was

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taken to prevent hemolysis and an effort was made to freeze the serum within several hours after its procurement. Most of the blood samples were obtained from patients seen at the Marion Davies Children's Clinic, U.C.L.A., the St. John's Hospital, Santa Monica, and Harbor General Hospital, Torrance.*

On each sample of serum the following determinations were made: mucoprotein-tyrosine, antistreptolysin 0 titer, C-reactive protein, and nonglucosamine polysaccharides. The method used for determining the mucoprotein-tyrosine was that of Winzler and associates[19] which gives results reportable as milligrams per cent tyrosine. The method used for the antistreptolysin determination was essentially that of Rantz and Randall,[23] with slight modifications as recommended by the manufacturer of the reagent.[20] The C-reactive protein determination was carried out with the precipitin method of Anderson and McCarty,[5] using commercially available antiserum.* The nonglucosamine polysaccharides were determined according to the original method of Shetlar and co-workers[21] with later modifications.[22]

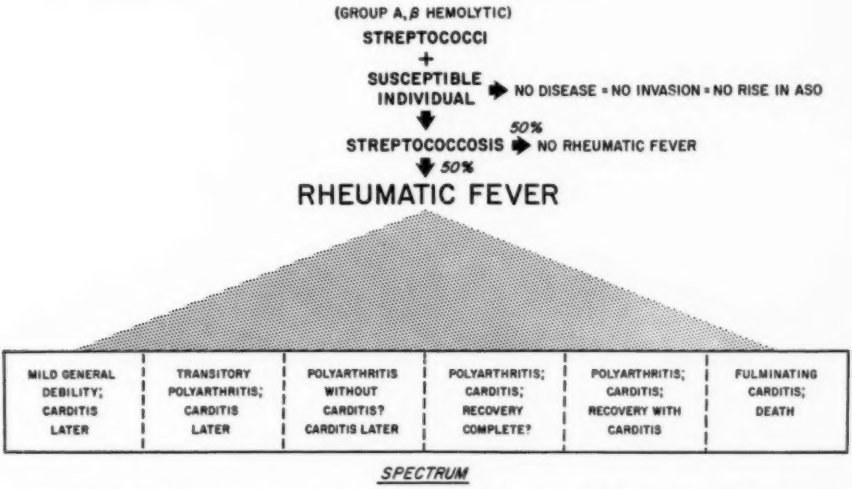

Fig. 1.—My interpretation of possible sequence of events following exposure of an individual susceptible to rheumatic fever to Group A, β-hemolytic streptococci. The three major responses are indicated: no disease; streptococcosis without rheumatic sequelae; and rheumatic fever. The spectrum of the disease is indicated at the bottom of the chart. It is my opinion that there is a shift to the left in subtropical climates and a shift to the right in temperate climates.

RESULTS

Normal Infants and Children.—Table I summarizes the results obtained on the sera from the seventy-six normal infants and children. The average mucoprotein-tyrosine was 3.3 mg. per cent, with a range of 1.8 to 4.3 mg. per cent. Because of some hemolysis in several samples, only sixty-seven of the sera were tested for antistreptolysin 0. The average titer

*I am indebted to Drs. Fink and Hodgman of the Los Angeles County Hospital for a number of the blood specimens, particularly on the patients with lupus erythematosus and rheumatoid arthritis.

*Kindly supplied by Schieffelin & Co., New York.

TABLE I. VALUES FOR ACUTE PHASE REACTANTS FOUND IN APPARENTLY HEALTHY CHILDREN

DETERMINATION	NUMBER OF INDIVIDUALS	AVERAGE	MINIMUM	MAXIMUM	MEASUREMENT
Mucoprotein-tyrosine	76	3.3 ± 0.5	1.8	4.3	Mg. per cent
Antistreptolysin 0 titer	67	55 ± 55	0	333	Todd units
C-reactive protein	76	0	0	2+	Mm. of precipitation
Nonglucosamine polysaccharides	75	116 ± 14	85	148	Mg. per cent

TABLE II. ACUTE RESPIRATORY DISEASE OF PROBABLE NONBACTERIAL ORIGIN

NAME	AGE (YR.)	MUCOPROTEIN-TYROSINE MG. PER CENT	ASO TODD UNITS	C-REACTIVE PROTEIN PRECIPITATE	NONGLUCOSAMINE POLYSACCHARIDES MG. PER CENT
J. T.	11	4.8	50	0	168
R. S.	7	6.0	50	2+	151
K. D.	11	5.0	12	1+	121
M. C.	10	4.7	50	0	141
E. A.	12	10.2	50	0	162
J. S.	11	5.0	125	0	120
V. M. B.	12	3.3	166	2+	111
M. W.	12	4.8	100	0	138
L. R.	10	4.0	50	1+	132
D. H.	6	4.5	12	0	177
E. S.	11	4.9	125	1+	114
B. G.	14	3.5	50	0	114
K. D.	10	4.0	12	0	139
D. D.	12	3.8	166	0	132
C. C.	6	3.7	125	1+	112
F. D.	8	3.6	12	0	109
L. C.	13	2.9	333	0	91
P. W.	10	3.3	50	1+	147
W. K.	10	3.2	50	–	127
C. B.	4	5.2	12	0	109
T. M.	12	3.9	125	0	117
S. F.	11	5.1	50	4+	124
P. T.	12	2.9	100	0	97
J. L.	2	5.3	166	0	153
R. T.	6	7.4	166	1+	159
C. D.	9	3.2	166	0	112
M. L.	14	2.7	125	0	135
D. J.	8	4.2	250	0	132
P. M.	7	5.1	50	0	145
Average	10	4.5 ± 1.5	97 ± 76	0 ± 1	131 ± 21
Range	2-14	2.7-10.2	12-333	0-4	91-177

was 55 Todd units, with a range of 0 to 333 Todd units. Of the seventy-six sera tested for C-reactive protein none was present in sixty-four, but twelve sera had 1 to 2+ precipitation. For the nonglucosamine determination the average value was 116 mg. per cent, with a range of 85 to 148 mg. per cent.

Infants and Children With Various Diseases.—Table II contains the individual data obtained from twenty-nine children with acute respiratory disease (ARD) of probable nonbacterial origin. The average values were as follows: aged 10 years, mucoprotein-tyrosine, 4.5 ± 1.5 mg. per cent; antistreptolysin 0, 97 ± 76 Todd units; C-reactive protein, 0 ± 1 mm. precipitate; and nonglucosamine polysaccharides, 131 ± 21 mg. per cent.

The results obtained on the seven patients with uncomplicated streptococcosis are shown in Table III. The average values were as follows: aged

12 years, mucoprotein-tyrosine, 4.1 ± 2.3 mg. per cent; antistreptolysin 0, 507 ± 460 Todd units; C-reactive protein, 2 ± 2 mm. precipitate; and nonglucosamine polysaccharides, 135 ± 14 mg. per cent.

Table IV contains the individual data obtained on fifteen children with acute rheumatic fever. In these instances the diagnosis was based on the clinical findings and was not contingent upon the results obtained from the acute phase reactants. The average values were as follows: aged 9 years, mucoprotein-tyrosine, 7.4 ± 2.0 mg. per cent; antistreptolysin 0, 533 ± 384 Todd units; C-reactive protein, 3 ± 2 mm. precipitate; and nonglucosamine polysaccharides, 180 ± 50 mg. per cent.

Table V contains the data obtained on seven patients with acute glomerulonephritis. All of the patients had hypertension, hematuria, albuminuria, and cylindruria. Unfortunately, cultures and typing for streptococci were not routinely done so it is impossible to state which of the cases were of streptococcal origin and of what type. The average values were as follows: aged 8 years, mucoprotein-tyrosine, 6.4 ± 2.2 mg. per cent; antistreptolysin 0, 314 ± 247 Todd units; C-reactive protein, 2 ± 3 mm. precipitate; and nonglucosamine polysaccharides, 184 ± 71 mg. per cent.

TABLE III. STREPTOCOCCOSIS

NAME	AGE (YR.)	MUCOPROTEIN-TYROSINE MG. PER CENT	ASO TODD UNITS	C-REACTIVE PROTEIN PRECIPITATE	NONGLUCOSAMINE POLYSACCHARIDES MG. PER CENT
T. C.	11	3.6	833	6+	121
C. P.	10	4.6	166	0	139
S. I.	12	3.0	250	1+	117
L. K.	6	3.6	1,250	0	135
C. R.	7	4.8	166	2+	148
K. B.	10	4.6	833	1+	---
J. S.	27	4.8	50	4+	150
Average	12	4.1 ± 2.3	507 ± 460	2 ± 2	135 ± 14
Range	6-27	3.0-4.8	50-1,250	0-6	117-148

TABLE IV. ACUTE RHEUMATIC FEVER

NAME	AGE (YR.)	MUCOPROTEIN-TYROSINE MG. PER CENT	ASO TODD UNITS	C-REACTIVE PROTEIN PRECIPITATE	NONGLUCOSAMINE POLYSACCHARIDES MG. PER CENT
C. B.	12	6.8	333	6+	169
L. B.	13	4.6	833	1+	142
D. B.	8	6.3	333	3+	203
S. A.	6	10.9	833	6+	235
W. T.	5	4.8	1,250	2+	203
D. E.	7	7.4	250	2+	172
L. Q.	15	9.3	250	1+	202
M. O.	12	8.5	833	0	162
N. C.	6	6.2	125	0	196
J. M.	7	6.0	1,250	4+	159
H. S.		5.8	166	3+	198
L. S.	12	5.8	250	1+	145
R. F.	11	9.9	625	5+	334
L. P.	12	9.6	166	6+	176
I. P.	6	9.7	500	3+	---
Average	9	7.4 ± 2.0	533 ± 384	3 ± 2	180 ± 50
Range	6-15	4.6-10.9	125-1,250	0-6	142 -334

TABLE V. ACUTE GLOMERULONEPHRITIS

NAME	AGE (YR.)	MUCOPROTEIN-TYROSINE MG. PER CENT	ASO TODD UNITS	C-REACTIVE PROTEIN PRECIPITATE	NONGLUCOSAMINE POLYSACCHARIDES MG. PER CENT
E. G.	11	6.3	500	6+	169
T. M.	10	5.8	166	0	---
R. O.	2	9.6	333	6+	264
J. L.	13	9.4	333	6+	204
J. L. V.	9	7.3	833	0	147
L. P.	3	4.0	166	0	184
M. G.	6	5.1	166	0	314
Average	8	6.4 ± 2.2	314 ± 247	2 ± 3	184 ± 71
Range	3-13	4.0-9.6	12-833	0-6	147-314

TABLE VI. ACUTE RHEUMATOID ARTHRITIS

NAME	AGE (YR.)	MUCOPROTEIN-TYROSINE MG. PER CENT	ASO TODD UNITS	C-REACTIVE PROTEIN PRECIPITATE	NONGLUCOSAMINE POLYSACCHARIDES MG. PER CENT
D. B.	1	10.8	0	6+	225
W. P.	5	12.8	0	6+	213
P. B.	3	6.7	50	1+	141
S. V.	11	5.8	12	1+	174
J. S.	7	6.4	0	3+	250
L. G.	2	14.6	0	6+	243
Average	5	9.5 ± 3.7	10 ± 20	4 ± 2	208 ± 40
Range	1-11	5.8-14.6	0-50	1-6	141-250

TABLE VII. INACTIVE RHEUMATIC FEVER

NAME	AGE (YR.)	MUCOPROTEIN-TYROSINE MG. PER CENT	ASO TODD UNITS	C-REACTIVE PROTEIN PRECIPITATE	NONGLUCOSAMINE POLYSACCHARIDES MG. PER CENT
J. B.	12	2.9	100	0	127
M. C.	11	3.1	50	0	123
D. B.	8	3.1	100	0	123
K. K.	12	2.7	12	0	121
C. B.	12	3.0	250	0	114
L. B.	13	3.6	100	0	126
P. C.	9	2.5	125	0	115
C. E.	8	3.7	0	0	100
J. H.	11	3.4	0	0	106
W. H.	14	4.0	125	1+	116
M. O.	12	2.6	166	0	142
N. C.	6	2.7	125	0	144
W. T.	5	2.5	125	0	110
Average	10	3.1 ± 0.4	98 ± 71	0	121 ± 13
Range	5-14	2.5-4.0	0-250	0-1	100-144

Table VI contains the data obtained on six children with acute rheumatoid arthritis. The average values were as follows: aged 5 years, mucoprotein-tyrosine, 9.5 ± 3.7 mg. per cent; anti-streptolysin 0, 10 ± 20 Todd units; C-reactive protein, 4 ± 2 mm. precipitate; and nonglucosamine polysaccharides 208 ± 40 mg. per cent.

Table VII contains the data obtained on thirteen children with inactive rheumatic fever. A number of these patients were the same on whom values were obtained during the acute phase of the disease but based upon clinical evidence were thought to be inactive at the time this blood sample

was obtained. The average values were as follows: aged 10 years, mucoprotein-tyrosine, 3.1 ± 0.4 mg. per cent; antistreptolysin 0, 98 ± 71 Todd units; C-reactive protein 0 mm. precipitate; and nonglucosamine polysaccharides, 121 ± 13 mg. per cent.

For the sake of brevity the data obtained on fifty-one children with various other conditions including lupus erythematosus, malignancy, asthma, allergic rhinitis, and obesity are summarized in Table VIII. In general, the acute phase reactant values were normal for the patients with asthma, allergic rhinitis, and obesity. In lupus erythematosus the mucoprotein-tyrosine and the nonglucosamine polysaccharides were elevated but the antistreptolysin 0 titer was normal; the serum from only one patient contained C-reactive protein. In malignancy all of the values were regularly elevated except for the antistreptolysin 0 titer.

Table IX contains a summary of the direction of results of the acute phase reactants in the various states.

TABLE VIII. OTHER DISEASES

DIAGNOSIS	NUMBER OF PATIENTS	AVERAGE AGE	AVERAGE MPT	AVERAGE ASO	AVERAGE CRP	AVERAGE NGA
Lupus erythematosus	4	30	6.2	79	0	166
Malignancy	6	7	7.6	258	4	187
Asthma	12	11	4.6	69	0	141
Allergic rhinitis	15	9	3.9	84	0	119
Obesity	14	13	4.1	86	0	138

TABLE IX. DIRECTION OF RESULTS OF ACUTE PHASE REACTANTS IN VARIOUS STATES

CONDITION	MUCOPROTEIN-TYROSINE	ANTISTREPTOLYSIN TITER	C-REACTIVE PROTEIN	NONGLUCOSAMINE POLYSACCHARIDES
Normal	Normal	Normal	0	Normal
Obesity	Normal	Normal	0	Normal
Asthma	Normal	Normal	0	Normal
Allergic rhinitis	Normal	Normal	0	Normal
Acute respiratory disease	Normal or slightly increased	Normal	±	Normal or slightly increased
Streptococcosis	Normal or slightly increased	Increased	±	Normal or slightly increased
Acute rheumatic fever	Increased	Increased	+	Increased
Acute glomerulonephritis	Increased	Increased	+	Increased
Acute rheumatoid arthritis	Increased	Normal	+	Increased
Inactive rheumatic fever	Normal	Normal	0	Normal
Malignancy	Increased	Normal	+	Increased
Lupus erythematosus	Increased	Normal	±	Increased

DISCUSSION

The combined data obtained in this study for normal infants and children and those with certain disease states agree well with that reported separately by others[1-16] for mucoprotein-tyrosine, antistreptolysin 0, and nonglucosamine polysaccharides. The presence of C-reactive protein in the sera from several apparently normal

individuals was an unexpected finding, however, as it is supposedly not present in sera from normal individuals. Unfortunately, one of the more commonly used acute phase reactants, the sedimentation rate, was not performed routinely during this study so its use is not being reported. Previous studies,[1, 3, 4] however, have shown that it parallels quite closely the serum mucoproteins except in certain unusual situations, namely, cardiac failure, nephrotic syndrome, and in patients on steroid therapy.

The physiological significance of all the acute phase reactants except the antistreptolysin 0 titer still remains obscure. The antistreptolysin 0 titer, of course, is specific for hemolytic streptococcal infection as it is a measure of the antibody response to the streptococcal antigen, streptolysin. Not all of the patients with streptococcosis reported in this study had elevated antistreptolysin 0 titers. In all likelihood this is because repeated blood samples were not obtained at intervals sufficiently long after the onset of the disease at a time when maximum antibody response should have occurred. It must also be remembered that not all patients with clear-cut streptococcosis show a rise in the antistreptolysin 0 titer.[11] The presence of a persistently low titer would make one doubt the possibility of a previous untreated streptococcal infection and also doubt the possibility of acute rheumatic fever. I am aware that determinations on a single sample of serum may not always be sufficient in order to establish the proper diagnosis. This is particularly true in differentiating prolonged uncomplicated streptococcal disease from mild rheumatic fever. In the former situation, all of the acute phase reactants might be slightly to moderately elevated, but the duration of the elevation is the differentiating factor. In streptococcal disease the mucoprotein-tyrosine seldom remains elevated longer than thirty days. In patients with clear-cut evidence of rheumatic fever[4] it was found that the mucoprotein-tyrosine seldom returned to normal sooner than three months after the onset.

From the data presented, it would appear that the C-reactive protein is a substance only remotely related to the mucoprotein-tyrosine and the nonglucosamine polysaccharides. Many patients had elevated values for mucoprotein-tyrosine and nonglucosamine polysaccharides without evidence of C-reactive protein being present, and vice versa. As a result of this observation and certain clinical observations, in my experience it would appear that the results of the C-reactive protein determination are less predictable and therefore probably of less value.

The data presented, on the other hand, might suggest that the mucoprotein-tyrosine and nonglucosamine polysaccharides are closely related or similar. Against this supposition is the fact that in a number of patients increases in the two components were not proportional. Likewise, data obtained during longitudinal studies on patients with rheumatic fever[24] failed to show consistently proportional changes when both values were plotted against each other as shown in Fig. 2. Although the two determinations likely represent different fractions, the usefulness of the nonglucosamine polysaccharide determination was so slight

that its performance no longer seems indicated.

The finding of essentially identical results of the acute phase reactants in the sera from patients with acute rheumatic fever and acute glomerulonephritis is not surprising. Epidemiologically, both diseases are thought to be related to infection by the beta hemolytic streptococcus, the main difference being that apparently only certain types of streptococci are nephrogenic, whereas all types of streptococci are thought to be rheumatogenic. Too few observations have been made on patients with uncomplicated Sydenham's chorea to be included in this presentation but certainly such should be done.

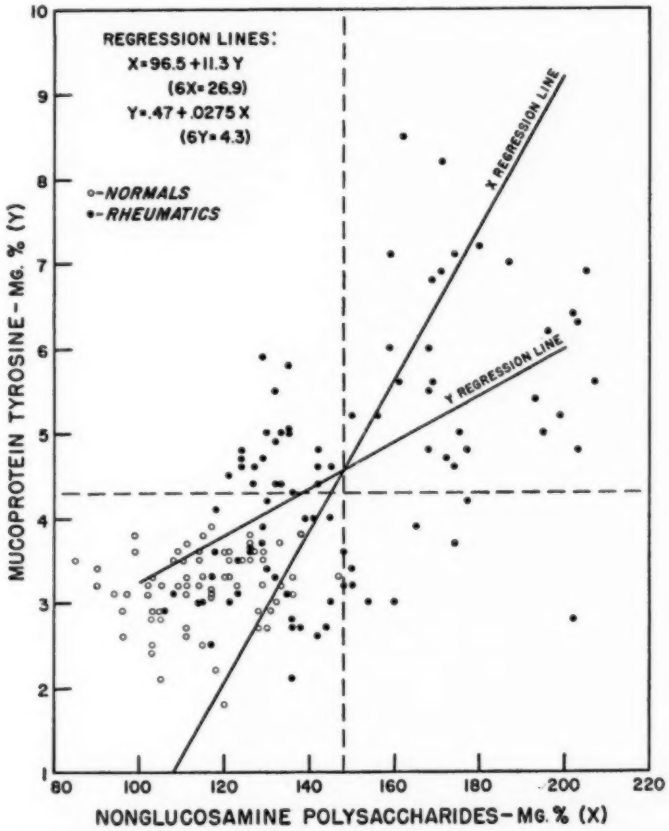

Fig. 2.—Each point on the chart represents the mucoprotein tyrosine and nonglucosamine polysaccharides value on the same sample of blood. The samples were obtained from seventy-one normal individuals and patients with acute rheumatic fever who were being followed during longitudinal studies. Note the lack of close correlation between the two tests.

It is interesting to note that the major difference between the sera from patients with acute rheumatic fever and acute rheumatoid arthritis is the normal antistreptolysin 0 titer in the

patients with rheumatoid arthritis. Although both diseases are generally classified as "collagen diseases," this difference suggests a different etiology for the two.

SUMMARY

Certain of the acute phase reactants were performed on the same sample of blood from individuals with the following states: normal, acute respiratory disease, streptococcosis, acute rheumatic fever, acute glomerulonephritis, acute rheumatoid arthritis, inactive rheumatic fever, lupus erythematosus, malignancy, obesity, asthma, and allergic rhinitis. Of the tests performed, the mucoprotein-tyrosine and the antistreptolysin 0 titer when done together appeared to be the most discriminating. It is suggested that the performance of such tests on the same sample of blood might aid in differentiating mild acute rheumatic fever and acute rheumatoid arthritis from each other and also from other disease states.

I wish to express my appreciation for technical assistance to Miss Barbara Reber.

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An Editor Is Not Infallible

The experiments of von Frich, of which we give an account elsewhere, are the most damaging arguments against Pasteur's preventive inoculations that have yet been brought forward. If, as now appears probable, the whole of Pasteur's claims are shown to be baseless, and all his inoculation work a mere conjuring with hypodermatic syringes and useless solutions, the collapse will be a tremendous one. Pasteur will have won a world-wide notoriety, secured honors, government appropriations, and thousands of dollars from private individuals, all through the glorification of a little operation which is futile, if not absolutely dangerous. Medical opinion upon Pasteur's work has uniformly been one of expectancy. From the very first it was recognized that his experiments were not demonstrative, nor his conclusions unassailable. The public, however, will be inclined to resent the whole affair as an imposition, if not downright quackery. This view will be natural, but at the same time unjust, for Professor Pasteur is beyond doubt sincere in his beliefs.

An editorial in THE MEDICAL RECORD, January 22, 1887.

Is Pasteur Also to Collapse? The announcement is made of two more deaths of patients who had been bitten by mad dogs and then inoculated by Pasteur. Among 54 persons bitten by mad wolves and inoculated by Pasteur, fourteen have now died, which is about the ordinary percentage. It seems impossible not to conclude that the Pasteur virus is at least impotent against mad wolves.

News Item from THE MEDICAL RECORD, 1886.

EVALUATION OF A NEW LIQUID DOSAGE FORM OF HYDROCORTISONE

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HYDROCORTISONE therapy may be indicated not infrequently in sick infants and small children. For this reason, a palatable liquid preparation of the hormone which is readily absorbed and produces satisfactory blood levels is desirable. Such an oral preparation might be administered more practically than tablets in many young patients. This study was undertaken in an attempt to compare the influence of a new liquid hydrocortisone preparation, hydrocortisone cyclopentylpropionate,† with compressed tablets of free hydrocortisone‡ on plasma and urinary 17-hydroxycorticosteroids and to determine the clinical effectiveness of this new dosage form.

EXPERIMENTAL

Effect of FCP on Plasma 17-OHCS in Dogs.—The responses of plasma 17-hydroxycorticosteroids (17-OHCS) to a dose of hydrocortisone cyclopentylpropionate (FCP) suspension equivalent to 20 mg. of hydrocortisone were determined in each of four fasted dogs. Plasma concentrations of 17-OHCS were determined by the method of Nelson and Samuels[1] before and at one-half, one, two, three, four, and five hours after the administration of the drug. These responses were compared with twenty-two observations from a similar experiment in which 20 mg. free hydrocortisone in tablet form had been given.

The data comparing the responses following the oral administration of equivalent doses of FCP and of free hydrocortisone are shown in Fig. 1. In each case following the administration of FCP, the maximum plasma 17-OHCS concentration occurred after one to two hours and was always less than the corresponding value observed after the administration of an equivalent dose of tablets of hydrocortisone. There was no indication of a prolonged elevation of plasma 17-OHCS concentrations.

Effects of FCP on Plasma and Urinary 17-OHCS in Human Subjects.—Each of seven normal young adult human volunteers was given a dose of FCP equivalent to 40 mg. hydrocortisone on one day and several days later was given 40 mg. free hydrocortisone tablets. On each day of the experi-

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Supported in part by a grant-in-aid from the Upjohn Company, Kalamazoo, Michigan.

*This work was done during the tenure of an American Heart Association Research Fellowship.

†Fluid Cortef, Oral Suspension, Upjohn.

‡C. T. Cortef, Upjohn.

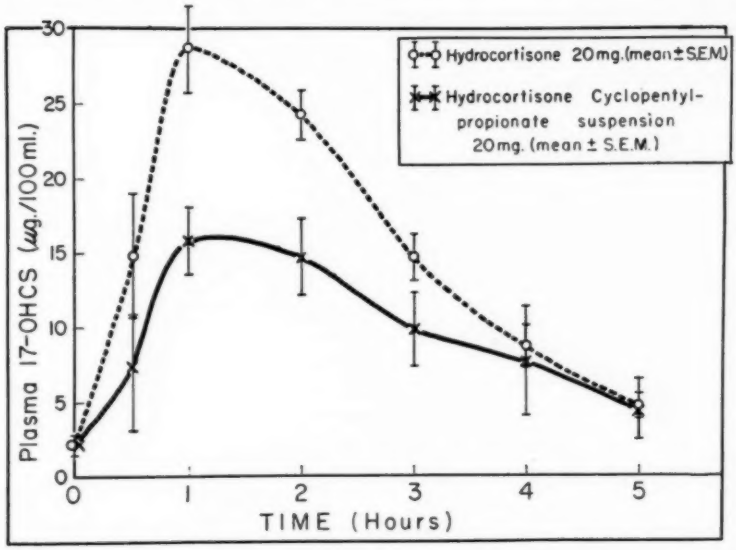

Fig. 1.—Comparison of effects of hydrocortisone cyclopentylpropionate suspension and hydrocortisone tablets on plasma 17-OHCS concentrations in dogs.

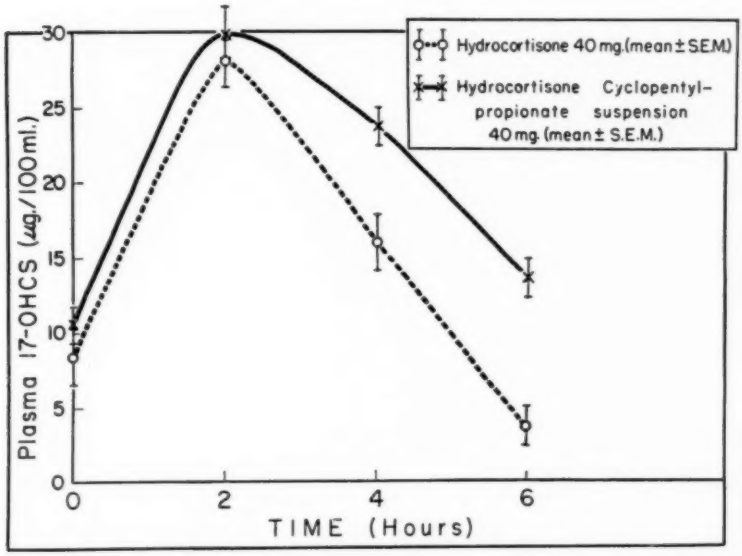

Fig. 2.—Comparison of effects of hydrocortisone cyclopentylpropionate suspension and hydrocortisone tablets on plasma 17-OHCS concentrations in human subjects.

ment blood samples were obtained immediately before and two, four, and six hours after the administration of the hormone preparation; urine was collected during a twelve-hour period following the administration of the drug. The specimens obtained were used for the determination of plasma 17-OHCS by the method of Nelson and Samuels[1] and urinary 17-OHCS by the method of Glenn and Nelson.[2]

As shown in Table I and Fig. 2 the results in human subjects differed considerably from those in dogs. In the human subjects, the plasma 17-OHCS concentrations observed at two hours after the administration of the FCP were, on the average, the same as the corresponding values following administration of free hydrocortisone. At the four- and six-hour intervals the values following administration of the former were somewhat higher than those following administration of the latter, indicating a more prolonged plasma steroid elevation with the FCP. Also, as shown in Table I, the urinary excretion of 17-OHCS during the twelve-hour period following administration of FCP was as great as that following administration of free hydrocortisone.

In vitro Experiments With FCP.—Certain experiments were carried out in an attempt to determine whether the material measured as 17-OHCS[1, 2] following the administration of the hydrocortisone ester, FCP, was the unaltered ester or free 17-OHCS.

TABLE I. COMPARISON OF EFFECTS OF COMPRESSED TABLETS OF HYDROCORTISONE (CTF) AND SUSPENSION OF HYDROCORTISONE CYCLOPENTYLPROPIONATE (FCP) ON PLASMA AND URINARY 17-OHCS

SUBJECT	DOSAGE FORM	PLASMA 17-OHCS (μG %)				URINE 17-OHCS (MG./12 HR.)
		0 HR.	2 HR.	4 HR.	6 HR.	
1	CTF	15.2	34.7	22.1	0.0	9.9
	FCP	10.7	32.6	22.4	12.2	6.2
2	CTF	6.6	38.5	12.6	5.5	7.8
	FCP	–	23.7	21.6	10.3	9.6
3	CTF	–	–	–	–	–
	FCP	11.5	24.2	19.7	18.8	–
4	CTF	6.3	12.9	11.2	5.7	4.6
	FCP	5.4	36.4	–	12.5	6.5
5	CTF	3.4	20.5	16.9	6.7	6.1
	FCP	9.3	29.8	28.7	13.1	5.9
6	CTF	7.3	–	12.4	4.9	4.8
	FCP	14.1	30.1	23.4	10.5	11.3
7	CTF	11.8	33.7	20.9	0.1	5.5
	FCP	11.4	32.3	26.5	18.2	5.5
Mean	CTF	8.3	28.1	16.2	4.0	6.3
	FCP	10.4	29.7	23.7	13.7	7.5

1. *Reaction With the Phenylhydrazine-Sulfuric Acid Reagent:* Known samples of FCP and of hydrocortisone acetate in 0.2 ml. of absolute ethanol were mixed with 0.4 ml. of the phenylhydrazine-sulfuric acid reagent[1] (reagent series). Duplicate samples were mixed with 0.4 ml. of sulfuric acid only (acid series). Color was developed for one hour at 60° C. and the samples cooled. Absorbance measurements were made according to the method of Bayliss and Steinbeck.[3] Results, calculated from the standard

curve for hydrocortisone with suitable corrections for molecular weight differences, are shown in Table II. Apparently, rapid hydrolysis of the esters occurred in the acidic medium and was followed by quantitative reaction with the reagent.

Table II. Determination of Hydrocortisone Esters by the Spectrophotometric Procedure

ESTER	TAKEN (γ)	FOUND (γ)	% RECOVERY
Cyclopentylpropionate	14.4	14.3	99.3
		14.5	100.7
	10.1	9.7	96.0
		10.2	101.0
	7.2	7.1	98.6
		7.1	98.6
	4.3	4.2	97.7
		4.3	100.0
		Average ± Std.Dev.	99.0 ± 1.6%
Acetate	13.1	12.9	98.5
		13.5	103.1
	9.2	9.0	97.8
		9.3	101.1
	6.5	6.6	101.5
		6.4	98.5
	3.9	3.9	100.0
		4.1	105.1
		Average ± Std.Dev.	100.7 ± 2.5%

Table III. Recovery of Hydrocortisone Esters From Florisil (From the 25 Per Cent Methanol-in-Chloroform Eluate)

COMPOUND	TAKEN (γ)	FOUND (γ)	% RECOVERY
Hydrocortisone	25.1	20.8	82.9
Hydrocortisone cyclopentyl-propionate	71.8	1.4	1.9
Hydrocortisone acetate	65.4	4.4	6.7

2. *Florisil Chromatography:* Duplicate samples of each ester were carried through the chromatographic procedure.[1] One set of residues from the 25 per cent methanol-in-chloroform eluates was examined by paper chromatography in the benzene-formamide system.[4] There was no evidence of production of free hydrocortisone and only traces of the esters were detectable. Analysis of the duplicate samples by the spectrophotometric procedure confirmed this observation. Recoveries are shown in Table III.

Attempt to Identify FCP in Human Plasma After Its Ingestion.—Each of two young adult males ingested FCP suspension equivalent to approximately 225 mg. of hydrocortisone. Two hours later blood samples were obtained and the plasma separated. The fibrin clot in each sample was expressed and the plasma extracted four times with 1.5 volumes of chloroform. The chloroform-extractable materials

were subjected to paper chromatography in the benzene-formamide system. The papergrams were observed after two hours (for the ester) and again after 96 to 102 hours (for free hydrocortisone) on the ultraviolet scanner. FCP was not detectable in either sample. The results are shown in Table IV.

Clinical Results With FCP.—On several different occasions it has seemed desirable to use a liquid oral administration form for hormone therapy in young patients. In these instances FCP has been employed in doses equivalent to those which would have been administered had hydrocortisone tablets been used. Although in most conditions it is extremely difficult to evaluate results of hormone therapy without large series of both treated and control patients, it has seemed that the FCP has been as efficacious as hydrocortisone might have been.

TABLE IV. PAPER CHROMATOGRAPHIC ANALYSIS OF PLASMA FROM PATIENTS WHO HAD INGESTED FCP

SUBJECT	PLASMA VOLUME (ML.)	ULTRAVIOLET ABSORBING AREAS
L. H.	19	More polar than FCP but less polar than hydrocortisone (10 γ) Hydrocortisone (20 γ) More polar than hydrocortisone (25 γ)
R. F.	20	Hydrocortisone (trace) Less polar than hydrocortisone (trace)

In patients with congenital adrenal hyperplasia it is possible to evaluate quite adequately the efficacy of therapy in a given individual. In this condition the immediate aim of therapy is to inhibit the release of ACTH by the pituitary and thereby reduce the production of adrenal androgens. Measurement of urinary 17-ketosteroid excretion before and during therapy serves as an accurate criterion of the adequacy of the therapy employed. Therefore, when the opportunity presented itself, FCP was employed in a previously untreated patient with this condition. This patient was a 13-month-old male with congenital adrenal hyperplasia (macrogenitosomia praecox), who had an older sibling with congenital adrenal hyperplasia (female pseudohermaphrodism). The diagnosis was made on the basis of the family history, excessive growth in height and weight, advanced bone age, high 17-ketosteroid excretion, low plasma levels and urinary excretion of 17-hydroxycorticosteroids, and failure of plasma 17-hydroxycorticosteroids to increase in response to ACTH stimulation. Previous to therapy the patient excreted between 11.4 and 15.0 mg. of 17-ketosteroids per day. After two weeks of therapy with FCP in doses equivalent to 50 mg. per day of hydrocortisone, his urinary excretion of 17-ketosteroids had decreased to 3.8 mg. per day. Since that time he has been maintained on a daily dose of FCP equivalent to 10 mg. per day of hydrocortisone.

DISCUSSION

Following the administration of FCP suspension to human subjects, the resulting peak elevations of plasma 17-

OHCS concentrations are equivalent to those following the administration of the same dose of hydrocortisone alcohol in tablet form. Subsequently, these elevations actually subside more slowly than do those following the administration of the free hydrocortisone. In addition, it appears that the urinary excretions of 17-OHCS are at least as great following the administration of FCP. This would suggest that the clinical effectiveness of the FCP suspension should be roughly equivalent to that of free hydrocortisone. As mentioned, from the preliminary results reported here it appears that this is the case.

The possibility was considered that perhaps the apparent elevations of plasma 17-OHCS concentrations observed following the administration of FCP might reflect measurement of the ester rather than free 17-OHCS. If this were the case, one could not predict the clinical effectiveness on the basis of the apparent plasma 17-OHCS concentrations since the esterified steroid cannot be assumed to exert the same physiological effects as the free steroid. The data regarding the reaction of steroid esters with the phenylhydrazine-sulfuric acid reagent (Table II) indicate that if the cyclopentylpropionate ester were present in the eluate from the chromatographic columns, it would be measured quantitatively as 17-OHCS. Apparently, rapid hydrolysis of the esters occurs in the acid medium employed for this color reaction. However, the data obtained when samples of the esters were carried through the chromatographic procedure indicate that even though the cyclopentylpropionate ester were present in the plasma sample it would not be present in the 25 per cent methanol-in-chloroform eluates from the chromatographic columns and therefore would not be measured as 17-OHCS by the technique employed. In addition, the paper chromatographic analyses of plasma samples obtained from human subjects following the administration of large doses of FCP indicated that no cyclopentylpropionate ester could be detected by this technique in the plasma of these subjects two hours after the oral administration of the test dose. Apparently, hydrolysis of the ester either occurred before absorption or was complete within two hours after absorption into the blood. In consideration of these data one may assume that the elevations of plasma and urinary 17-OHCS concentrations observed in this study do not reflect measurement of the cyclopentylpropionate ester.

It is not possible on the basis of present data to explain adequately the differences observed between dogs and human subjects with regard to the comparative effects of FCP and of free hydrocortisone on plasma 17-OHCS. Whereas FCP in human subjects produced plasma 17-OHCS elevations which were as great as and more persistent than those produced by free hydrocortisone, this was not true in dogs. In these animals the steroid elevations produced by FCP were not as great as those produced by equivalent doses of free hydrocortisone and there was no evidence of prolongation of these elevations. Since the data presented indicate that the technique employed measures only free 17-OHCS in the blood and that probably hydrolysis of the ester occurs before absorption from the intestine, these differences in response between dogs and human subjects suggest that the rate

of hydrolysis of the ester in the intestinal tract is probably slower in the dog than in man. In this regard, it has been observed that orally administered hydrocortisone acetate (in doses up to 6 mg. per kilogram) does not elicit a physiological response in the dog,[5] suggesting possible failure to hydrolyze this ester. In the human subject, a lower order of therapeutic effect is obtained with hydrocortisone acetate than with hydrocortisone, although the ester does lead to elevated plasma 17-OHCS concentrations.[6] The data presented indicate that Fluid Cortef is a satisfactory oral dosage form for the human subject.

SUMMARY

1. Plasma 17-OHCS concentrations attained after administration of hydrocortisone cyclopentylpropionate (FCP) in dogs and in human subjects were compared with those attained after administration of free hydrocortisone. Although in dogs the elevations attained after the former were not as great, in human subjects they were of equal magnitude and greater duration than those attained after administration of free hydrocortisone.

2. After administration of FCP, the elevated plasma 17-OHCS concentrations do not reflect measurement of unhydrolyzed ester. Although the cyclopentylpropionate ester does react quantitatively with the phenylhydrazine-sulfuric acid reagent, it is not measurable by the technique employed since it is not present in the 25 per cent methanol-in-chloroform eluate from the chromatographic column. In addition, paper chromatographic analysis of plasma of human subjects two hours after administration of FCP failed to reveal any trace of this ester in the plasma.

3. Preliminary clinical observations indicate that FCP is a satisfactory administration form for hormone therapy in the young patient.

We are indebted for technical assistance to Doris F. Tippit, H. Beth Dowding, Mary C. O'Brien, Tiona L. Hughes, and Esther B. Nadolski.

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CORTICOTROPINS IN THE TREATMENT OF TRANSIENT SYNOVITIS OF THE HIP IN CHILDREN

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TRANSIENT synovitis of the hip joint is a symptom complex that is common in pediatric practice. It is the most frequent cause of limp due to pain and muscle spasm around the hip joint which we have observed.

A survey of the literature reveals a dearth of recent observations. Finder[5] reported on twenty-two patients, Rauch[8] on thirty-seven, Edwards[4] on thirteen, and Butler[1] on nineteen. However, most authors state that the disease is common. In a discussion on Hermel and Sklaroff's[6] paper in the 1954-1955 *Year Book of Pediatrics,* Silverman states, "We have seen over 100 children with the clinical picture described within the past few years." Donaldson[2] reports fifty-two consecutive cases of children treated on the orthopedic service in the Children's Hospital, Pittsburgh, Pennsylvania. He, too, states that it is the most commonly recognized cause of pain in the hip in children between 3 and 10 years of age.

The clinical picture has been well described. The onset may be sudden; the patient screams with pain when he bears weight or moves the leg. It may be more gradual. The parent simply notices a little limp when the child walks. Sometimes a previously well child awakens with pain in the leg and refuses to move from the bed. We have particularly noticed that the majority of our patients had their first symptoms upon awakening, either in the morning or after a nap. These typically are pain and limp, usually in a male child between the ages of 3 and 10 years.

On physical examination significant findings are usually confined to the hip. These children do not appear ill. When the patient is supine he usually holds the hip flexed. The test described by Rauch has been of great service in detecting muscle spasm around the hip, which we have always found: "Abduction and internal rotation are investigated with the patient in the supine position. For the performing of internal rotation, while one extremity is completely extended and untouched the other is flexed at the hip until the thigh is perpendicular to the body; then with the knee also flexed to a right angle and fixed by the left hand of the examiner, the ankle is grasped by the examiner's right hand and moved directly outward. The movement is in effect an internal rotation of the femoral head. Pain is usually evinced when this is tried on the involved extremity."

Roentgenographic studies have been reported by Drey[3] and by Hermel and Sklaroff.[6] We have not found roentgenograms useful, except in a

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TABLE I. SUMMARY

DATE	AGE (YR.)	SEX	HISTORY ALLERGY	INFECTION PRESENT	TRAUMA	TIME BEFORE TREATMENT	PREVIOUS TREATMENT	HIP INVOLVED	SYMPTOMS
6/ 7/55	6½	M	Father hay fever	Slightly red throat	No	5 hr.	None	Right	Spasm Limp Pain
6/17/55	6	M	Both parents	U. R.	No	20 hr.	None	Left	Spasm Limp Pain
6/21/55	4¾	M	None	Acute throat infection	No	3 da.	None	Right	Spasm Limp Screams when touched
8/16/55	2½	F	None	None	No	3 hr.	None	Right	Spasm Limp Pain
8/23/55	4	M	Mother hay fever	None	No	6 hr.	None	Left	Spasm Limp Pain
9/ 8/55	3	M	None	Throat infection	Yes Fall 2 days ago	1 da.	None	Left	Spasm Limp Pain
9/13/55	5	F	Unknown	Throat infection	No	12 hr.	None	Left	Limp, pain on manipulation
9/17/55	6	M	Father asthma	No	No	32 hr.	Antibiotics Heat	Right	Spasm Limp Pain, severe
10/13/55	5	M	Child asthmatic	No	No	8 hr.	None	Right	Spasm Limp Pain

*Acthar gel, Armour.

negative sense, to help in excluding certain other conditions.

As the title implies, this is usually a self-limited symptom complex. Treatment has been simply rest in bed, with traction for only severe cases. Relief of signs and symptoms has usually taken from four to twenty-one days. Donaldson gave his patients complete bed rest with split Russel traction for several days; then 40 per cent were put in a hip spica for six weeks. The other 60 per cent were kept at complete bed rest for one or two weeks longer. He states that transient synovitis may be a first stage of Calve-Legg-Perthes' disease.

The ten white children reported here are all private patients. They were all seen during a four-month period from June to September, 1955, at office visits or house calls; none were hospitalized. Nine are summarized in Table I. The tenth case was observed by Dr. Sims Chapman. Eighty units of ACTH was given in this case. Complete relief was obtained in twenty-four hours.

Steinberg and Roodenburg reported complete relief of five cases of acute

OF CASES REPORTED

TEMP. RECTAL (° F.)	WBC	SED. RATE (MM. HR., WINTROBE)	RG HIPS	CORTICOTROPINS* ACTH	RESPONSE
99.4	11,600 70% segs.	2	Neg.	ACTH 40 units Cortisone 75 mg. total	Relief pain ½ hr.; complete response 24 hr.
99.4	8,200 48% segs.	6	Neg.	ACTH 120 units, 3 doses Cortisone 300 mg. total	Relief pain ½ hr.; complete response 8 hr.
100.0	8,800 50% segs.	12	Neg.	ACTH 40 units Cortisone 75 mg. total Cortisone 200 mg.	Complete relief in 24 hr. Relapse after 24 hr. Fell off tricycle Response in 72 hr.
99.0	13,400 52% segs.	21	Neg.	ACTH 80 units Cortisone 250 mg.	Complete response in 3 hr.
98.8	7,900 48% segs.	4	Neg.	ACTH 80 units Cortisone 300 mg.	Complete relief symptoms within 3 hr.
101.0	13,750 30% segs.	10	Neg.	ACTH 80 units Cortisone 120 mg.	Complete relief 24 hr.
100.0	12,250 42% segs.	4	Neg.	Cortisone 100 mg.	Incomplete relief of limp in 24 hr. Complete relief 72 hr.
102.0	12,200 57% segs.	12	Neg.	ACTH 80 units Cortisone 300 mg.	Relief pain in 9 hr. Complete response in 22 hr.
99.4	-	-	Neg.	ACTH 80 units Cortisone 100 mg.	Response in 6 hr. Complete response in 2 da.

subacromial bursitis within a few hours after ACTH had been given. The clinical course of this bursitis is similar to that of transient synovitis and thus suggested this treatment to us.

The results following our treatment regimen have been most gratifying. The parents can be told with a reasonable assurance that within four or five hours the pain would be relieved and within twenty-four hours the limp gone. No restrictions of exercise or weight-bearing were imposed. Only two of the children failed to respond this well. One child was given cortisone again after twenty-four hours because his limp recurred; the other's symptoms persisted for about seventy-two hours. The initial dosage of ACTH varied from 40 to 120 units, with the total cortisone dosages varying from 75 to 300 mg. The "give-and-watch" method was our guide to dosage schedule.

The clinical response to corticotropins has been so consistent and gratifying, even in this small experience, that we felt obliged to record these observations and to suggest that this form of therapy impresses us as a most welcome relief from older

regimens of prolonged rest and traction. Also this might be proposed as a simple therapeutic test: if prompt response is not obtained or if recurrences appear, re-evaluation is in order. In such a situation, we do not feel that empiric or symptomatic treatment with corticotropins should be continued.

SUMMARY

A clinical report on the use of only corticotropins in the treatment of transient synovitis of the hip in children is presented. Gratifying responses prompted this brief note on the use of ACTH and cortisone in the treatment of clinically apparent synovitis of the hip in ten children.

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A SYNDROME SIMULATING ENCEPHALITIS AFFECTING CHILDREN RECOVERING FROM MALNUTRITION (KWASHIORKOR)

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MALNUTRITION is common in South African Bantu (Negro) children. As in other parts of the world, it is caused by diets consisting mainly or entirely of cereals and lacking milk or other foods of animal origin. The clinical features of infantile malnutrition have been described during the past two decades under such titles as kwashiorkor,[1] infantile pellagra,[2] and malignant malnutrition.[3] Severe cases are characterized by retarded growth, edema, angular stomatitis, cheilosis, and a specific dermatosis. The scalp hair of the Negro child, which is normally black, thick, and curly, turns grayish-brown, thin, and straight, while the skin changes from dark brown to a light-brown color. Moderate to severe liver damage is usually found in these cases.

This type of nutritional disorder responds well to treatment with diets consisting mainly or exclusively of cow's milk, and most of the above-mentioned deficiency signs disappear within three to four weeks.

Apart from some mental irritability, neurological disturbances are rare in these patients. However, in a previous communication[4] a syndrome was described which occurs on rare occasions some six days to several weeks after the faulty diet of the child has been changed to a high-protein diet. This syndrome has never been observed in children other than those recovering from malnutrition; neither has it been seen in children who are still severely ill with malnutrition.

Briefly, the syndrome consists of coarse tremors, parkinsonian in type, which affect most commonly the upper extremities and also, though less frequently, the legs, the neck, the tongue, and the facial and abdominal muscles. In some cases the whole body is shaken by tremors which cease, though not always entirely, during sleep.

As a rule, these children are a little irritable, but there is no clouding of consciousness.

In some cases the upper extremities are held in a peculiar position: the arms are abducted at the shoulders and flexed at the elbows; the hands are pronated and deviated toward the ulnar side, and the thumb is flexed into the semiclosed palm.

The extremities may show evidence of "cogwheel" or "lead-pipe" rigidity. The lower jaw may sag, lending the face a vacant expression, but there is no excessive salivation.

The tendon reflexes are nearly always abnormally brisk. In severe cases there may be myoclonus in one or

From the Baragwanath Hospital and the Coronation Hospital.

TABLE I. CLINICAL

	CASE 1	CASE 2	CASE 3	CAS
Month of admission	September	January	February	Ja
Age	7½ mo.	14 mo.	19 mo.	9 mo.
Sex	Female	Male	Male	Ma
Diet leading to malnutrition	Watery corn (maize) porridge	Corn (maize) and some milk	Corn (maize) and 8 to 12 ounces cow's milk daily	Corn (mai
Weight on admission	8½ pounds	18 pounds	19 pounds	9¾ poun
Signs of malnutrition on admission to hospital	Depigmentation of skin and hair; hair atrophic; diarrhea and dehydration	Nutritional edema; atrophic scalp hair; had diarrhea 14 days before onset of tremors	Atrophic hair; depigmentation of skin	Nutritiona Gross em Nutritiont Psis
Treatment given for malnutrition	Dehydration corrected with intravenous therapy; feeding formula based on dried skimmed milk; no vitamins	Skimmed milk formula prepared from powdered skimmed milk; no vitamins	Mixed diet	Mixed die Milk
Interval between change to satisfactory diet and onset of tremors	11 da.	10 da.	3 wk.	12 da.
Manifestations of the syndrome	Severe tremors of arms, head, and tongue; worse on left side of body; myoclonus left hand; lead-pipe rigidity; exaggerated tendon reflexes	Tremors of both arms and left leg; exaggerated tendon reflexes; hallucinations (?)	Tremors of both hand head, and abdomina muscles; rigidity of arms; exaggerated tendon reflexes	Tremors Muscles, Hands (v left); ab Posture Arms; m Weakness Ability; i Tendon r Drooping
Duration of tremors	11 da.	10 da.	3 wk.	1½ mo.

more of the limbs, producing a jerking movement at a rate of about one every second. The myoclonus may continue during sleep.

Less frequent components of the syndrome are muscular weakness, opisthotonus, excessive sweating, and insomnia.

The cerebrospinal fluid is normal in all respects.

The prognosis of the syndrome is almost invariably good, the patient returning to normal within a few days to several months. However, one patient reported on previously[4] shows now, some three years after cessation of tremors, evidence of mild hemiplegia, mental retardation, and major epilepsy.

In this paper eight more cases of the syndrome are reported. It will be shown that they conform to the clinical picture described previously and that they confirm the previous observation that this condition occurs only during recovery from malnutrition. In an attempt to elucidate the pathogenesis of this neuropathy, a number of investigations have been carried out which are presented in some detail.

TABLE I. CLINICAL DATA

	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8
...y		October	December	August	October
...	... mo.	3 yr.	14 mo.	17 mo.	16 mo.
...	...le	Male	Female	Male	Female
... and ...	...n (maize)	Corn (maize) rarely some milk	"Baby food" consisting to 50% of corn (maize)	Corn (maize)	"Baby food" consisting to 50% of corn-flour (maize)
...	...¾ pounds	26 pounds	14 pounds	15½ pounds	14 pounds
...; depig...	...tritional edema; ...ross emaciation; ...utritional derma... ...osis	Nutritional edema; sparse atrophic scalp hair; cheilosis, stomatitis, diarrhea	Scalp hair atrophic; smooth tongue; depigmentation of skin	Scalp hair sparse and atrophic; depigmentation of skin	Scalp hair sparse and atrophic; skin and hair depigmented; nutritional edema and dermatosis
...	...ixed diet plus ...ilk	Mixed diet plus milk and vitamins	Skimmed milk and other food; also vitamins	Milk and vitamins	Milk and vitamins
...	...2 da.	31 da.	14 da.	Several weeks	13 da.
...th han... ...domina... ...lity of ...rated ...s	...remors of facial ...uscles, jaw, neck, ...ands (worse on ...eft); abnormal ...osture of both ...rms; muscular ...eakness; irritability; increased ...endon reflexes; ...drooping of jaw	Severe tremors of both arms and both legs; slight mental irritability	Tremors of neck, arms, and abdominal muscles; slight tremor of legs; abnormal posture of arms; exaggerated tendon reflexes	Tremors of arms and legs; slight cogwheel rigidity; exaggerated tendon reflexes; mental irritability	Severe tremors of neck, arms, and left abdominal muscles; cogwheel rigidity of arms; lead-pipe rigidity of legs; drooping of jaw
...	...½ mo.	3 wk.	1 mo.	2 mo.	2½ mo.

THE PRESENT SERIES

The present series is composed of four patients from Baragwanath Hospital, where the original eight patients were treated, and four from Coronation Hospital. Clinical details of these patients are shown in Table I.

There was no seasonal preponderance in the incidence of the syndrome. Three of the patients were girls and five were boys. The youngest in this series was 7½ months old and the oldest was 3 years. In all patients the state of malnutrition which preceded the syndrome could be attributed to a faulty diet consisting largely of corn (maize), the staple cereal of the poorer population in this area.

Before the appearance of tremors these patients did not differ, either in the clinical picture of malnutrition or in the course followed during convalescence, from others who recover without developing neurological complications.

The syndrome started from seven to thirty-one days after the children had

been changed to a satisfactory diet. In three patients the diet consisted of a formula prepared from dried skimmed milk; in two patients, a formula prepared from fresh skimmed milk; and in three patients, a mixed diet which included full-cream fresh milk.

Four patients had not received vitamin supplements with the improved diet, but the remaining four had been given (after admission to hospital and before the onset of tremors) daily doses of 3,000 units of vitamin A, 500 U.S.P. units of vitamin D, 1.5 mg. of thiamine hydrochloride, 1.2 mg. of riboflavin, 10 mg. of nicotinamide, 40 mg. of ascorbic acid, and 2.5 μg of vitamin B_{12}. In addition, two of the four children had received daily injections of 5 mg. of pyridoxine hydrochloride, 5 mg. of calcium pantothenate, and 20 μg of vitamin B_{12}.

Fig. 1.—A patient (Case 4) suffering from the syndrome. Note drooping of lower jaw and the characteristic posture of the upper extremities.

As in previous cases, tremors were the most striking feature of the syndrome. They were coarse and resembled those occurring in parkinsonism. They varied in intensity, distribution, and duration as indicated in Table I. In two patients (Cases 4 and 6) the tremors persisted during light sleep. One (Case 1) had myoclonus of the left arm for a period of four days, and two patients (Cases 4 and 6) showed evidence of abnormal posture of the arms.

Fig. 2.—Same patient as shown in Fig. 1 eight weeks later. Tremors have ceased, but the arms are still slightly abducted at the shoulders and flexed at the elbows. The mouth is open.

All patients were irritable when disturbed, at least during the first few days after the onset of tremors. There was no clouding of consciousness in any of the children, but it is possible that one patient (Case 2) suffered

from frightening hallucinations for several days.

Tendon reflexes were grossly exaggerated except in two patients (Cases 5 and 8), in whom they were normal. In the older children (Cases 3, 4, 5, and 8) the plantar reflexes were consistently flexor.

The syndrome cleared up completely within ten days to six weeks in all but one patient (Case 5), in whom tremors continued for two and one-half months, and abnormal posture of the arms and drooping of the jaw were still recognizable for some weeks after the cessation of the tremors.

Laboratory investigations concerning the eight patients are listed in Table II. The majority of these data were collected after the syndrome had commenced, but those shown in parentheses were obtained before the onset of tremors.

The cerebrospinal fluid was examined in five of the eight patients. It was normal cytologically and biochemically.

In six of the patients, blood examinations revealed a mild normochromic normocytic anemia. This responded to a high-protein diet with a reticulocytosis and a rise in hemoglobin (Cases 3 and 8).

Serum albumin levels were low, and serum globulin and gamma globulin levels were normal or high.

Flocculation tests for liver function were positive, except in two patients (Cases 6 and 8), who showed little or no abnormality.

Serum cholinesterase values were low in three out of four cases. Serum bilirubin levels were normal.

In one patient (Case 8) the nonprotein nitrogen level of the blood was abnormally low on arrival at the hospital, but it rose to normal values after treatment with a high-protein diet had begun and after the syndrome had made its appearance. In the same patient the blood ammonia level was normal while the syndrome was at its height.

Fasting blood sugar was determined in two cases and was within normal limits.

Serum potassium, sodium, and calcium levels were entirely normal.*

Electroencephalograms were carried out on two patients (Cases 4 and 7), and they were indistinguishable from those of normal children of similar age.

The effects of certain therapeutic measures on the syndrome were studied in several patients. Two (Cases 5 and 6) received a low-protein diet for six and ten days, respectively, but this did not influence the syndrome. In other cases the intravenous injection of glucose, calcium chloride, and pyridoxine hydrochloride were equally ineffective. One patient (Case 4) was given 1 Gm. of methionine daily for four days, and two (Cases 5 and 8) received 4 Gm. of glutamic acid daily for five days, in all instances without visibly influencing the intensity of the tremors.

DISCUSSION

The eight cases presented in this paper conform to the criteria of the syndrome described previously,[4] the only noteworthy differences being that this series includes three girls (all patients in the first series were boys)

*Above abnormalities of blood and serum are typical of infantile malnutrition (kwashiorkor).

TABLE II. SUMMARY OF INVESTIGATIONS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE (5)	CASE 5	CASE 6	CASE 7	CASE (8)	CASE 8
Cerebrospinal fluid										
Polymorphonuclears (per c.mm.)		Nil	Nil	1				Nil		Nil
Lymphocytes (per c.mm.)		2	1	5				Nil		3
Protein (mg./100 ml.)		14	13	38				11		18
Sugar (mg./100 ml.)				52				44		60
Blood										
Hemoglobin (grams/100 ml.)	8.0		9.4		(10.3)	11.5	10.6	10.8	(8.5)	10.7
Reticulocytes (%)			6.5							4.0
Mean corpuscular hemoglobin concentration	32					31	31			32
Packed cell volume (%)	26					37	34			33
Total white cells (per c.mm.)	7,000		12,700		(8,900)	10,200	9,500	12,400	(8,500)	7,000
Neutrophils (%)	26		22		(32)	33	32	74		30
Lymphocytes (%)	67		71		(65)		61	22		65
Serum										
Total protein (grams/100 ml.)	6.5		6.3		(4.1)	7.1	7.5	5.7	(3.5)	5.6
Albumin (grams/100 ml.)	3.4		2.6		(2.1)	3.2	3.7	2.4	(1.1)	2.6
Globulin (grams/100 ml.)	3.1		3.7		(2.0)	3.9	3.8	3.3	(2.4)	3.0
Gamma globulin (grams/100 ml.)			1.5			1.3	1.54	1.41		0.96
Thymol turbidity (units)			8.5	9.0		6.0	2.5	4.0	(6.5)	6.0
Thymol flocculation			++++	++++		++++	Neg.	++++	(+++)	Neg.
Colloidal red test			+	+		+	Neg.	+	(+)	Neg.
Takata-Ara test				+		+		+		
Total lipids (mg./100 ml.)						392		372		
Alkaline phosphatase (K-A units)			11.8	11.6		19.2	16.0	16.0		18.2
Cholinesterase (% of average normal)						86	100	52		83
Bilirubin: Direct (mg./100 ml.)						0.1	0.1	0.2		0.2
Bilirubin: Total (mg./100 ml.)						0.3	0.3	0.4		0.5
Miscellaneous tests										
Nonprotein nitrogen (mg./100 ml.)				32					(13)	33
Blood ammonium (μg/ml.)										0.64
Blood sugar (mg./100 ml.)							74	60		82
Wassermann reaction	Neg.						Neg.			Neg.
Serum potassium (meq./L.)							4.5			
Serum sodium (meq./L.)							135.0			
Serum calcium (meq./L.)						5.1	4.5	4.9		
Electroencephalogram				Normal				Normal		

Data shown in parentheses were obtained before the onset of tremors.

and that the age limits were wider, the youngest patient being 7½ months and the oldest 3 years of age (previous age limits were 10 months and 2½ years).

The cases in this series were typical in that the syndrome commenced some days or weeks after the physical condition of the malnourished children had improved in response to a high-protein diet. Before the onset of tremors these patients did not differ clinically from the average severe case of malnutrition seen in this area. The syndrome was, therefore, an unpredictable complication of the recovery from malnutrition.

As in the previous series,[4] the tremors ceased entirely after a few weeks or months; but in one patient (Case 4) an abnormal posture of the arms and sagging of the lower jaw persisted for several weeks after cessation of tremors.

The investigations shown in Table II did not help to elucidate the pathogenesis of the syndrome, because the data do not differ in any respect from those encountered in other children with malnutrition who are not suffering from the syndrome.

The cause of the syndrome remains obscure. Originally it was suggested that this condition was the result of an imbalanced repair process produced by a diet rich in protein but deficient in vitamins.[4] This view is no longer tenable, because four children in the present series had been receiving satisfactory vitamin supplements before the onset of tremors. The diet used in the treatment of malnutrition does not play a part in the causation of the syndrome, because three children developed tremors while taking a formula based on dried skimmed milk, two while receiving a formula based on fresh skimmed milk, and three while taking a mixed diet.

There was no evidence that electrolyte disturbances were concerned in the causation of the syndrome.

Our cases are apparently distinct from the portal-systemic encephalopathy reported by Walshe[5] and Sherlock and associates.[6] The patients described by these authors showed evidence of severe hepatic dysfunction, whereas in two of our patients flocculation tests for liver function displayed little or no abnormality, and the livers of three patients in the previous series[4] showed no marked pathological changes on microscopic examination. The cases of Sherlock and co-workers[6] were characterized by raised blood ammonia levels; this test was carried out in one patient (Case 8) of the present series and was found to be within normal limits. Blood urea levels were normal in two of our patients, indicating satisfactory detoxification of ammonia in the liver. Furthermore, clouding of consciousness was a feature of the cases described by the authors mentioned, while our patients were lucid throughout their stay in the hospital, with the possible exception of one patient (Case 2), who seemed to be suffering from frightening hallucinations for a few days. Finally, while the administration of methionine and glutamic acid or a change to a low-protein diet influenced the course of the portal-systemic encephalopathy, no such changes could be detected in our patients in response to similar treatment.

The syndrome is not confined to our two hospitals. Isolated examples have

been encountered in widely separated areas of Africa.[7-11] Moreover, in Italy, Gerbasi[12, 13] reported identical neurological phenomena in malnourished infants, but he did not state whether the disorder started after the malnutrition had been treated or whether it was seen in untreated cases.

Gerbasi suggested, probably with justification, that his patients suffered from the "acute cerebral tremors" described by Zappert in 1909.[14] The latter reported eighteen cases, thirteen boys and five girls, aged 8 months to 2 years, all showing coarse tremors of sudden onset which lasted up to three months. The case histories of these children indicate the occasional presence, in addition to tremors, of abnormal postures of the limbs, myoclonic jerks, irritability, insomnia, and excessive sweating.

Zappert did not attribute this neuropathy to malnutrition, probably because nutritional disorders were still poorly defined and understood in his days. However, one of the patients in his series was wasted, one was suffering from "physical debility" and two from "dyspepsia" (Finkelstein's synonym for the term malnutrition), one had been fed on small amounts of beer, and six were suffering from a variety of alimentary upsets. It is, therefore, not unlikely that malnutrition played a part in the causation of Zappert's cases.

In this part of Africa the association of the syndrome with the recovery phase of malnutrition has now been observed in a significant number of cases and further confirmation of this etiological relationship may be gleaned from the fact that all the recorded cases have occurred in the Negro population, where nutritional disorders are common, and that no cases have yet been encountered among the 350,000 white inhabitants of Johannesburg, where malnutrition is rare.

Although the dependence of this neurological syndrome on malnutrition can now be considered as securely established, the question of the exact pathogenesis remains unsolved.

SUMMARY

This paper contains eight case reports of a neurological syndrome previously observed and described by one of us in children recovering from malnutrition. The syndrome consists of coarse tremors, postural abnormalities, exaggerated tendon reflexes, myoclonus, and a number of less constant components. Recovery usually takes place within a few weeks.

It is at present unknown why the syndrome develops in some children but not in others who are recovering from equally severe attacks of malnutrition.

Investigations have shown that this syndrome is not related to the portal-systemic encephalopathy seen in association with severe liver damage. The exact pathogenesis of the condition is obscure.

It is suggested that the syndrome is identical with the "acute cerebral tremors" described by Zappert in 1909, and it is shown that Zappert's cases were probably associated with malnutrition.

We wish to thank Miss O. L. Abrahams and Mrs. R. Kitai, of the General Hospital Laboratory, for the blood ammonia determinations on one patient (Case 8).

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Caecil County, Maryland, May 11, 1772.

I have often been astonished at reading the Boston News, having generally in it very interesting occurrences, of accidents and providence, &c among which acts of providence, they tell us of one on the 23d of April last, viz. that the wife of Mr. Stetson, of Braintree, was delivered of her fourth pair of Twins, and two single births within eight years—I suppose that was communicated to the public, in order to agrandize Mr. Stetson's ability and character, and more especially as a gentleman of that place. And if it becomes practicable, that such Feats be communicated to the public, I think with no less propriety may I inform the public, that the wife of Richard Dobson, near the head of Elk, was delivered of five children in fifteen months, three still born children, and at another birth Twins. And of a gentlewoman, near Whiteclay-creek, New-Castle County, who was delivered of four live-born children at one birth, and in twenty months after of Twins. These two matters are real facts; and unless the gentlemen of Boston and the Northward, can out-strip us here of the Southward, I beg they may not cram the News-papers with such inconsiderable matter.

From PENNSYLVANIA GAZETTE.

THE TREATMENT OF COMMON ANEMIAS IN INFANCY AND CHILDHOOD WITH A COBALT-IRON MIXTURE

Including a Case Report of Iron Deficiency Anemia Due to Geophagia

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THE occurrence of some degree of anemia is a frequent finding in infants and children at the time of routine hospital admission. In the absence of a well-defined blood dyscrasia, there is a tendency to regard these anemias as relatively inconsequential. Iron is sometimes prescribed on the assumption that iron deficiency is often present in the growing child. Ordinary hematinic agents are of little use if the anemia is one which accompanies chronic disease or infection, and the only satisfactory remedy has been thought by many to be the correction of the basic etiology. It is then expected that the hemopoietic system will correct the anemia.

It should be recognized, however, that vigorous treatment of these anemias can be beneficial, regardless of the type which may be present. It is logical to assume that better tissue nutrition and a consequent possible improvement in resistance to disease would result from correction of anemia. For example, Coles[6] points out that although the anemia of infection is seldom severe, it "favors the development of further infection and may retard convalescence."

There is considerable literature on the experimental use of cobalt in producing polycythemia in laboratory animals, and its use as a therapeutic agent in the treatment of human anemias was first reported twenty-five years ago.[32] The recent development of cobalt-iron therapy in this country now makes it possible for the clinician to attack the problem aggressively.

Cobalt has been proved to be a powerful stimulant to the erythropoietic tissue of the bone marrow. In simple iron deficiency, the accelerated erythropoiesis produced by cobalt appears to create an iron demand which may, in turn, increase the absorption of iron.[9] Furthermore, cobalt maintains the rate of hemopoiesis at the maximum physiologic level until normal values are attained,[27] thus producing a more rapid over-all response than do simple iron salts alone.

These results have led many investigators to use cobalt salts in the treatment of different types of anemias. Reports have dealt with its use in nutritional anemia, anemia of prematurity and multiple births, pregnancy anemias, anemias associated with infections and malignancies, anemia associated with chronic renal disease, and in the hemolytic anemias.[2, 4, 6-8, 10, 11, 14-17, 21-23, 25, 28, 29, 32, 34-38] Although bone marrow studies were reported by some

From the Driscoll Foundation Children's Hospital.

of these investigators, the first such studies in children with anemia of infection or "alimentary anemia" were reported by Virdis[30] in 1952. He successfully correlated the improved peripheral blood findings with accelerated erythropoiesis in the marrow. Where infection or chronic disease is present and responsible for inhibition of hemopoiesis, cobalt possesses the unique property of overcoming the inhibition.[11, 34, 36] Although iron, per se, may not be of specific value in treating this anemia, practically all children can well afford an increased increment of iron. Cobalt-iron therapy would seem, therefore, to be well suited to treatment of anemia in children, due to this cause.

In the past five years a number of clinical reports have appeared describing satisfactory results in adults and children with different types of anemia treated by a cobalt-iron mixture.[3, 7, 15, 16, 23, 26, 27] We have had five patients with iron deficiency anemia due to dirt-eating (geophagia), all of whom were treated for several months with iron alone without showing the desired effect. Subsequently, these five patients were treated with a cobalt-iron preparation with very good results. This observation led us to use cobalt-iron therapy in different types of anemia in children.

It is the purpose of this paper to present our experiences with cobalt-iron therapy in the anemias commonly encountered in pediatric practice. The fifty cases reported in this paper were followed over a period of three years; all had iron deficiency anemias of varying etiology, including the five cases of "dirt-eaters," of which one will be discussed in detail.

METHODS AND MATERIALS

This study is based on observations of fifty infants and young children with anemia. All were followed either in the outpatient clinics and pediatric wards of the Santa Rosa Hospital, San Antonio, or the Driscoll Foundation Children's Hospital, Corpus Christi, Texas. About one-half of all patients were followed in the outpatient clinics, the others in the hospital. The twenty-seven females and twenty-three males in the series ranged in age from 1 month to 11 years, with more than one-half under 1 year. Three patients were Negroes (Cases 6, 9, and 19, (Table I), four were premature infants (Cases 47, 48, 49, and 50), and one single twin (Case 44).

Hemoglobin determinations were made by the acid hematin method with the Haden-Hausser instrument. Hematocrit values, red cell counts, white cell counts, reticulocyte counts, and differential white cell counts were done according to methods described by Wintrobe. Sedimentation rates were done by the Cutler micromethod. Bone marrow biopsies were made from the iliac crest, sternum, or tibia. The slides were prepared and stained with Wright's stain. Patients received the cobalt-iron preparation orally, in either liquid or tablet form.* The daily dosage provided 20 to 40 mg. of cobalt chloride with 37.5 to 75 mg. of ferrous sulfate (except in a single instance) in 0.3 or 0.6 ml. of solution, respectively, in children under 5 years of age (forty-three cases), and 45 to 60 mg. of cobalt chloride with 0.6 to 0.8 Gm. exsiccated ferrous sulfate in enteric-coated tablets for those over 5 years of age (seven cases). Practically all of

*The cobalt-iron preparations used in this study were supplied as Roncovite, by Lloyd Brothers, Inc., Cincinnati, Ohio.

TABLE I. HEMOPOIETIC RESPONSE OF SEVERAL TYPES OF CHILDHOOD ANEMIAS TO COBALT-IRON THERAPY

CASE NO.	AGE	DOSAGE: COBALT CHLORIDE (MG./DA.)	DOSAGE: FERROUS SULFATE (MG./DA.)	DURATION OF THERAPY (WK.)	HEMOGLOBIN (GM./100 ML.): INITIAL	HEMOGLOBIN (GM./100 ML.): FINAL	RBC ($\times 10^6$/MM.^{3}): INITIAL	RBC ($\times 10^6$/MM.^{3}): FINAL	BODY WEIGHT (KG.): INITIAL	BODY WEIGHT (KG.): FINAL
				Anemia With Geophagia						
1	4 yr.	40	75	12	10.0	11.5	4.10	5.17	16.90	17.80
2	3 yr.	40	75	9	8.0	13.0	3.28	4.10	10.20	11.00
3	16 mo.	40	75	11	9.5	11.5	3.90	5.15	7.62	8.21
4	2 yr.	40	75	14	6.5	11.0	4.36	4.60	12.00	13.33
5	18 mo.	40	75	11	8.5	12.0	3.60	4.90	8.20	8.80
				Nutritional Anemia						
6	12 mo.	40	75	7	3.5	10.5	2.88	3.96	8.18	8.89
7	2 mo.	20-40	37½-75	10	7.5	12.0	2.60	4.30	3.15	4.56
8	1 mo.	20-40	37½-75	5	9.0	13.5	2.67	4.59	2.70	5.72
9	4 yr.	40	75	5	7.5	11.5	4.04	4.92	12.30	14.29
10	11 mo.	40	75	5	10.0	12.5	4.31	4.61	6.60	7.62
11	14 mo.	40	75	8	8.0	11.0	4.99	5.80	7.53	9.48
12	5 yr.	45*	0.6 Gm.*	4	9.0	11.0	3.72	4.42	13.65	15.24
13	8 yr.	45*	0.6 Gm.*	5	8.5	11.0	3.96	5.09	20.77	22.00
14	10 yr.	60*	0.8 Gm.*	14	6.5	12.0	3.75	4.19	24.40	27.71
15	3 yr.	40	75	5	9.0	12.5	4.28	5.05	11.20	12.70
16	3 yr.	40	75	9	10.0	11.5	3.95	4.65	11.43	12.07
17	9 yr.	45*	0.6 Gm.*	6	10.5	11.0	4.06	4.68	22.04	22.95
18	7 mo.	40	75	4	10.5	11.5	4.00	4.30	6.35	6.71
19	18 mo.	40	75	4	1.6	11.5	1.43	4.17	8.18	8.50
				Anemia Associated With Infection						
20	9 mo.	40	75	9	9.5	12.5	3.43	5.34	4.40	5.72
21	7 mo.	40	75	8	8.0	11.5	3.70	4.00	5.30	6.60
22	12 mo.	40	75	5	10.0	11.0	3.91	4.33	5.60	7.53
23	12 mo.	40	75	14	6.0	10.5	4.35	4.94	8.30	10.43
24	3 mo.	20-40	37½-75	5	10.5	11.0	3.73	3.96	3.30	3.90
25	8 yr.	45*	0.6 Gm.*	7	7.0	10.5	4.62	4.81	21.00	20.55
26	8 mo.	40	75	6	7.5	10.5	3.73	4.60	6.65	6.60
27	2½ mo.	20-40	37½-75	9	9.5	14.5	3.29	5.21	3.45	3.90
28	8 mo.	40	75	4	9.5	11.5	3.98	5.19	6.23	6.85
29	10 mo.	40	75	5	8.0	11.0	5.19	5.29	6.86	8.03
30	2 mo.	20-40	37½-75	10	9.0	11.0	3.75	3.92	4.56	6.80
31	10 mo.	40	75	4	9.5	13.0	3.36	4.70	5.03	6.71
32	14 mo.	40	75	7	9.0	11.0	4.52	4.97	7.06	8.48
33	2 mo.	20-40	37½-75	9	8.5	10.5	3.60	3.79	2.58	3.76
34	2 yr.	40	75	9	8.5	11.5	4.68	5.25	8.98	10.12
35	8 yr.	45*	0.6 Gm.*	12	10.0	11.2	3.86	4.09	25.70	25.76
36	8 yr.	45*	0.6 Gm.*	12	9.5	12.5	3.28	4.43	21.77	21.91
37	4 mo.	20-40	37½-75	8	9.0	10.5	5.21	5.60	4.81	5.35
38	4 yr.	80	150	5	7.0	10.5	2.58	3.99	14.56	15.20
39	4 mo.	40	75	5	9.0	13.0	3.30	4.55	3.67	4.40
40	20 mo.	40	75	4	9.0	12.5	3.35	5.10	9.48	10.07
41	5 mo.	40	75	4	6.0	10.0	2.45	3.39	4.15	4.58
42	12 mo.	40	75	9	5.0	12.0	4.26	4.40	7.60	9.65
43	4 mo.	40	75	10	9.5	12.0	4.19	4.40	5.15	6.18
				Anemia Associated With Prematurity and Multiple Births						
44	12 mo.	40	75	12	10.5	11.0	3.53	4.60	3.65	8.44
45	3mo.	40	75	15	9.0	13.5	4.06	4.28	4.12	6.70
46	4 mo.	40	75	13	10.0	14.0	3.92	4.50	4.56	7.26
47	6 mo.	40	75	14	7.5	11.5	3.46	5.12	3.30	4.12
48	5 mo.	40	75	12	8.0	12.5	4.24	4.98	2.46	3.88
49	2 mo.	40	75	16	8.5	13.0	3.98	4.66	1.98	3.26
50	3 mo.	40	75	12	9.5	13.5	4.16	5.20	2.63	4.58

*Tablet form cobalt-iron preparation: each tablet contains 15 mg. cobalt chloride and 0.2 Gm. exsiccated ferrous sulfate.

the infants and children in this study took the cobalt-iron mixture quite readily, either alone or when added to either the formula, fruit juice, or cereal. The tablet form was taken with water immediately after meals. Where a simple iron preparation was administered, children aged 5 years or less received a total daily dose of 150 to 225 mg. of ferrous sulfate and older children received 330 to 495 mg. of this substance. Both were in the form of commercial liquid preparations. The diagnostic criterion of anemia was arbitrarily set at any hemoglobin level below 11.0 Gm. per 100 ml. (76 per cent). The diagnosis of geophagia in our five cases was confirmed by roentgenographic demonstration of amorphous material in the colon. This technique has previously been described by Clayton and Goodman.[5]

RESULTS

The cases as shown in Table I can be classified in four groups as follows:

1. Anemia with geophagia ("dirt-eating") in five cases (Cases 1 to 5).
2. "Nutritional anemia" in fourteen cases (Cases 6 to 19).
3. Anemia associated with infection or other disease in twenty-four cases (Cases 20 to 43).
4. Anemia associated with prematurity and multiple births in seven cases (Cases 44 to 50).

The clinical history and subjective findings at the time of initial examination of all patients were as follows:

The presenting symptoms included poor weight gain or loss of weight (forty-two cases), anorexia (thirty-two cases), retarded physical development (twenty-eight cases), irritability (twenty-six cases), easy fatigability (eighteen cases), inactivity or subnormal activity (sixteen cases), and lethargy (nine cases).

On physical examination all patients showed a marked pallor of the skin, mucous membranes, and nail beds. Twenty-two patients displayed evidence of malnutrition, three of very severe degree (Cases 6, 19, and 44). Some retardation in development was apparent in nineteen patients. Although primarily physical, some mental retardation was obvious in a few of these. Hepatosplenomegaly was found in seven and hemic murmurs were found in five of the patients. Treatment was continued for ten to sixteen weeks in eighteen patients, and for four to nine weeks in thirty-two patients (Table I). During this time, forty-seven of the patients received neither transfusion nor therapy with other hematinic agents. Eight of the group had previously been treated with iron alone, without clinical response (see Table II). One had failed to respond to vitamin B_{12} therapy. Each of three patients received two small whole blood transfusions at the time of admission (Cases 6, 19, and 42). Hemoglobin values of only about 7 grams were present on the second day (Cases 6 and 42) or third day (Case 19) after transfusion, at which time therapy was begun.

It has been observed by others that a fall in hemoglobin and erythrocyte levels frequently occurs within a few days to a week after transfusion.[24] However, in our series, the three patients who received transfusions on admission and then were treated with cobalt-iron showed a continued rise in hemoglobin and erythrocyte values. Blood counts as shown in Table I were taken at the beginning and completion

of cobalt-iron therapy. In these three cases repeated blood counts two weeks after cobalt-iron therapy was discontinued showed no essential change.

In the three transfused patients, bone marrow biopsies were performed initially and after concluding cobalt-iron therapy. In all cases a pronounced increase in the total cells of the erythroid series was present, presumably as a result of cobalt medication. One of these (Case 19) was especially interesting, with an initial severely hypoplastic marrow in which erythropoiesis was reduced or arrested at the erythroblastic stage. After forty-five days of cobalt-iron therapy the marrow showed moderate erythroblastic and normoblastic hyperplasia with a myeloid-erythroid ratio of 3:1. Although all cells of the erythroid series were increased, this finding was especially notable in the numbers of proerythroblasts and in basophilic, polychromatic, and oxyphilic normoblasts.

The initial dosage of 0.6 c.c. of the liquid cobalt-iron preparation caused minor gastrointestinal intolerance in seven patients (Cases 7, 8, 24, 27, 30, 33, 37) all 4 months of age or less. This dosage represented 40 mg. of cobalt chloride and 75 mg. of ferrous sulfate. Accordingly, the dosage was promptly decreased to 0.3 c.c. and then increased at weekly intervals to the patient's level of tolerance or to the point of hemopoietic response. It did not exceed in any case, however, the 0.6 c.c. dose.

The patients were observed carefully during the course of therapy for the presence of any toxic manifestations. During the entire period, significant side effects were noted in only two patients. They complained of loose stools, with accompanying nausea and vomiting of four to five days' duration (Cases 32 and 42). These symptoms persisted for three to four days after therapy was discontinued. Two days after the above symptoms ceased, a second trial of cobalt-iron therapy was instituted at the higher dosage levels, with no recurrence of gastrointestinal symptoms. *Salmonella typhi* was discovered in a stool culture of one patient (Case 32).

In eight cases, as shown in Table II, we administered the simple iron preparations described above over a period of from five to twelve weeks.

TABLE II. HEMATOLOGIC RESPONSE TO COBALT-IRON MEDICATION IN CHILDREN FAILING TO RESPOND TO IRON THERAPY

PATIENT	AGE	DURATION OF THERAPY (WEEKS)		INITIAL BLOOD VALUES		VALUES AFTER TREATMENT			
						AFTER IRON		AFTER COBALT-IRON	
		IRON*	COBALT-IRON†	RBC/ (MIL./ C.MM.)	HB. GM./ 100 ML.)	RBC (MIL./ C.MM.)	HB. (GM./ 100 ML.)	RBC (MIL./ C.MM.)	HB. (GM./ 100 ML.)
1	4 yr.	8	12	4.6	10.0	4.1	10.0	5.17	11.5
2	3 yr.	7	9	3.1	7.5	3.28	8.0	4.1	13.0
3	16 mo.	7	11	3.85	9.0	3.9	9.5	5.15	11.5
4	2 yr.	5	14	4.0	6.5	4.3	6.5	4.6	11.0
5	18 mo.	5	11	3.2	9.0	3.6	8.5	4.9	12.0
11	14 mo.	8	8	4.6	7.5	4.9	8.0	5.8	11.0
34	2 yr.	12	9	3.9	7.5	4.68	8.5	5.25	11.5
44	12 mo.	8	12	3.3	10.5	3.53	10.5	4.6	11.0

*Dose of ferrous sulfate used = 150 to 225 mg. ferrous sulfate per day.

†Dose of cobalt-iron mixture (Roncovite drops) = 20 mg. cobalt chloride, 37½ mg. ferrous sulfate per day, increasing to 40 mg. $CoCl_2$ and 75 mg. $FeSo_4$ as a maximum.

These patients were then given cobalt-iron medication for an additional period (eight to fourteen weeks). It is quite evident from Fig. 1 and Table II that the response to the cobalt-iron mixture exceeded that of the simple iron preparation.

Fig. 1 shows the hematologic response of a typical case of iron-deficiency anemia (geophagia) treated unsuccessfully with iron, but followed by a prompt rise in erythrocytes, hemoglobin, and reticulocytes upon the institution of cobalt-iron medication.

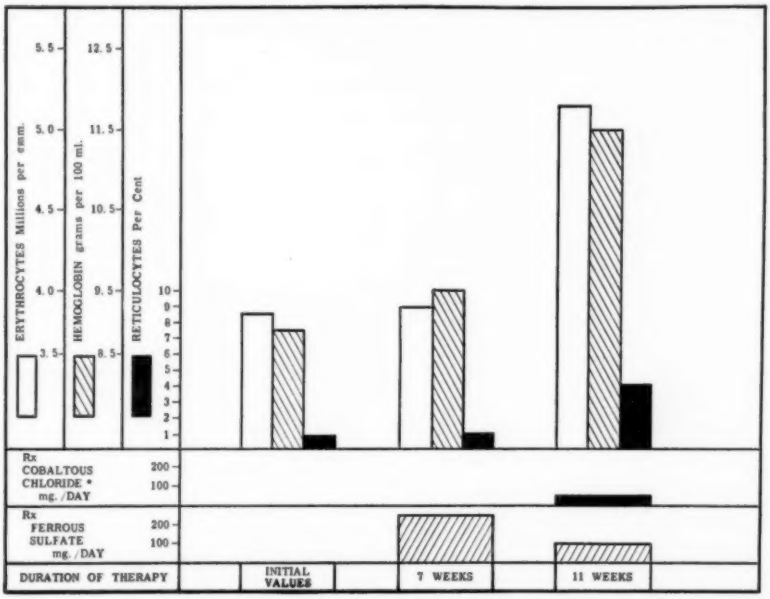

Fig. 1.—Hematologic response of Patient A. C. to iron and to subsequent cobalt-iron medication. *When cobaltous chloride was begun both the cobalt and ferrous sulfate were given as Roncovite.

The case report for the patient shown in Fig. 1 is as follows:

CASE REPORT

A. C. was a 16-month-old white female, showing symptoms of weakness, pallor, constipation, loss of appetite, and weight loss. The patient was one of three siblings, all giving a past history of geophagia. (Two others are reported as Cases 1 and 2, Table I). The family history was noncontributory. Maternal history revealed a normal full-term pregnancy, normal delivery, and normal neonatal course. The child's dietary habits showed a distaste for green vegetables and fruits, and the desire for a preponderance of milk-containing foods in the diet. There was no dietary supplementation of vitamins and iron. At the time of admission, the history revealed sand and "dirt eating" for the past four months, with the child refusing regular food with the exception of milk. During the month directly preceding admission, the parents noted a grayish pallor of the child's skin. Examination of a gastric specimen revealed no free hydrochloric acid. X-ray examination of the abdomen showed opaque shadows and some amorphous material

in the colon, no doubt resulting from the ingestion of sand and dirt.

The clinical findings of the four additional cases of hypochromic microcytic anemia associated with geophagia were approximately the same as those reported above. Three negative stool examinations for ova and parasites were obtained on each of these cases. Each of the above cases showed hypochlorhydria or achlorhydria and positive x-ray findings. Further details concerning the clinical manifestation of geophagia will be published elsewhere.

DISCUSSION

The most common anemia of childhood is iron-deficiency anemia. This may result from the unusually large requirement of iron necessary to support growth, from an inadequate dietary intake, from poor gastrointestinal absorption, or from a failure of the hemopoietic system to utilize iron during or after infection. The response to iron administration in iron-deficiency anemia is generally accepted as being uniformly satisfactory. In practice, however, particularly in pediatrics, two important factors may present obstacles to prompt acceptable therapeutic results.

First the consistency and magnitude of the response to iron is, in a large degree, proportional to the dosage used. Intolerance in infants and children is often so great a problem that it restricts the daily dosage to levels far below the optimum. The result is a relatively slow, often unsatisfactory rate of hematologic recovery. In our experience, cobalt-iron therapy was not subject to this major disadvantage. A number of commercial preparations for pediatric use have solved the problem of tolerance simply by providing ineffective doses of iron.

Second, the absorption of iron in infants and children may be less uniform and consistent than in adults. In fact, on the assumption that this factor is responsible for much of the iron-deficiency anemia seen in children, the term "nutritional anemia" has often been applied as a separate entity. Some authorities believe that normal gastric acidity is necessary for optimal absorption of iron and that hypoacidity or achlorhydria are important factors contributing to iron deficiency in infants and children. In this connection it is interesting to note that all of our cases of geophagia presented hypochlorhydria (Cases 3 and 5) or achlorhydria (Cases 1, 2, and 4). Since cobalt has been shown to correct anemia following gastrectomy,[13] it would seem that cobalt influences iron absorption favorably even in the absence of gastric acidity. On this basis, it is not surprising that cobalt-iron medication was effective in the anemia of geophagia where hypoacidity was present.

It is also of importance to consider that children, and particularly artificially fed infants between 6 months and one year of life have no appreciable iron stores and an infection of a few weeks' duration can cause an anemia due to repression of iron utilization. This anemia tends to lower body resistance and a cycle of temporary or perhaps even continuing ill health is established. Such common childhood conditions as pyelitis, cystitis, bronchitis, tuberculosis, etc., can all contribute to the establishment of an anemic condition of this sort.

The results of cobalt-iron therapy in patients with anemia associated with infection (Table I) were uniformly good. In our patients, these anemias

were found associated with monilia infection, chronic suppurative otitis media, pyelitis, pulmonary tuberculosis, malaria, bronchitis, bronchopneumonia, meningitis, osteomyelitis, varicella, or other infections of unknown origin.

The results shown in Table II indicate that certain cases of iron-deficiency anemia do not respond to the administration of iron alone. In Cases 1 to 5, geophagia was present, Case 11 appeared to be a simple "nutritional" anemia, and Case 44 was a hypochromic anemia due to multiple birth. Although bronchitis was seen in Case 34, a marked hypochromic anemia was present and some response to iron might have been expected.

On the other hand, the striking superiority of cobalt-iron therapy is well illustrated in Table II by the data which show that these same patients responded far more rapidly and completely to cobalt-iron therapy. It should be noted that this was true even though the liquid cobalt-iron preparations supplied significantly less iron than did the simple iron preparations. It must be assumed, therefore, that the improvement in response was due essentially to the cobalt component of the medication.

Data in Table I indicate the consistency and uniformity of the response to cobalt-iron therapy and, in a sense, these results may be compared with the data in Table II if we consider the iron-treated group as "controls."

The over-all results tabulated in Tables I and II indicate that cobalt-iron therapy is useful in treating both the anemia due to iron deficiency and that associated with other disease etiologies.

Previous clinical experience suggested to us that patients with anemias of the type represented in Table I suffered a marked inhibition of growth and development. Preliminary experiments with cobalt-iron therapy suggested to us that growth and development were accelerated with a more rapid correction of the anemic condition. Consequently, weight gains were recorded and are shown in Table I. The gain in weight shown supports our view that these anemias inhibit body growth and development, and that correction of the anemia is essential to a restoration of normal body metabolism. These gains in weight are also evidence of the lack of toxicity of the cobalt-iron mixture used.

The mechanism by which cobalt exerts its hemopoietic effect is not thoroughly understood. Diverse reports in the literature have suggested that cobalt may act by inhibiting sulfhydryl groups in enzyme systems,[1] by affecting the catalase activity of the liver,[31] by peripheral vasodilatation,[19] by decreases in blood volume due to diuresis,[20] or by the production of arterial hypotension,[18] but much additional, equally good evidence has been presented to contradict these suppositions. This subject has been fully discussed by Warren and associates[33] and Grant and Root.[12] There can be little doubt that a direct stimulation of erythropoiesis results from the administration of cobalt, and whether this action is a direct one upon the marrow elements, as suggested by Coles,[6] or whether it is mediated through other unknown mechanisms is a question which must await further study. In any event, lack of toxicity seems well established and, in our opinion, cobalt-iron therapy is a safe and useful therapeutic

agent which provides the clinician with a means of attacking the problem of the common anemias in infants and children.

SUMMARY

Problems concerned with iron therapy make it somewhat less than satisfactory treatment in children, even in simple iron deficiency anemia. Iron, of course, is of little or no value in anemia associated with infection or chronic disease.

Cobalt possesses the property of causing direct stimulation of hemopoiesis. This appears to be of clinical value in improving the response to iron in iron-deficiency anemia. The same property makes it possible to carry on aggressive treatment of those anemias due essentially to the hemopoietic depression which accompanies certain common diseases of children.

In a general way, children feel better and gain weight during cobalt-iron medication, and such direct treatment of these anemias is recommended both in iron-deficiency and as an adjunct to specific therapy.

Anemia associated with geophagia, "nutritional" anemia, anemia associated with infection, and the anemia associated with prematurity and multiple births responded, in our patients, to cobalt-iron therapy.

Cobalt-iron therapy is, in our opinion, a useful, safe therapeutic agent for routine use in the treatment of most of the common anemias of infancy and childhood.

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Habit Training 500 Years Ago

Healthy children have good habits and do not complain. When children whine or cry they are unhealthy, therefore, one should consider their health and care for them in such a manner that they contract no bad habits. One should with great industry see that they do not have unusual movements and if they whine or cry or are angry one should take care to see why they are so and try to prevent it. Children cry either because they have pain, or are troubled, or because they are wet with urine, or wish to go to stool, or they are too hot or too cold, or have too many clothes on, or have lain too long or they are lying in unclean covering. All these things should be considered and whatever is necessary should be done for the child. Above all things their linen should be kept clean. When one would comfort or quiet a child it can be done in three ways. First, put the mother's breast in its mouth as when one gives the child the breast all its troubles are put to one side; secondly, with song, for a mild voice reaches its heart; and thirdly, that one softly rocks the cradle.

It also should be understood that when children begin to creep around the floor and to reach after things one should make for them a little pen of leather so that they do not hurt themselves. And finally one should never leave them long and unprotected.

From Bartholomaeus Metlinger, 1473.

THE FIGHT AGAINST INFECTIOUS HOSPITALISM IN A CHILDREN'S NURSERY AND HOSPITAL

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THE dangers inherent in a lengthy sojourn in a children's nursery or hospital are twofold: (1) diseases the child may contract in a hospital environment (infectious hospitalism) [4, 5, 8, 19, 25, 35, 39, 41, 50, 51] and (2) psychomotor difficulties due to a long sojourn away from the family environment (psychic hospitalism).[7, 26]

We recently discussed methods employed at the Clinique des Nourrissons in Geneva, Switzerland, to avoid psychic hospitalism.[26] We shall now report on the means which have seemed best to us to fight against infectious hospitalism. Since our conclusions are based on several thousands of days, we feel they indicate a method of protecting infants from the inconveniences linked to a too lengthy sojourn in a hospital environment.

OUR RESEARCH

The Clinique des Nourrissons is an institution which accepts children with contagious diseases and nutritional difficulties, or other specific affections, as well as newborn, premature, and healthy infants.

The presence of these two categories in the same building lodging twenty-five children who are cared for not only by registered but also by student nurses creates certain complicated problems. We have endeavored to solve these problems mainly by studying the arrangement of the rooms, the equipment of the nursery and hospital, and the distribution of the children in the various wards.

The patients with communicable diseases are kept in an isolation ward on the ground floor, completely separated from the rest of the nursery and hospital by a door which is locked with a key. The nurses go in and out by means of a door leading to the outside. Children with whooping cough and even measles have been treated in this ward without the complication of an epidemic in the rest of the nursery and hospital.

The ground floor also includes four rooms for children being treated for digestive difficulties. The healthy boarders are also kept there, taking into account the duration of their stay and especially their age. The rooms can hold a maximum of three to five children.

Finally, the top floor is equipped according to the plan published by the Cradle Society, Evanston, Illinois, U.S.A.[40, 42] (Fig. 1.) This installation, intended especially for the premature, newborn, and feeble children, constitutes a unit including six small compartments, each one separated from the others by glass walls 2 meters high, and each one opening

From the Clinique des Nourissons and the Service de Bactériologie Institut d'Hygiène.

into the same corridor. The air, humidified at 50 per cent by vapor and maintained at 23° C. in summer by an air conditioning apparatus, is disinfected day and night by ultraviolet rays.* In this ward, the nurses wear masks, and between each compartment they change aprons and disinfect their hands by washing with soap and then soaking them a minute in a disinfectant.†

We have found this installation superior to the rooms on the ground floor; for a period of five years we noted the number of days during which the infants have had febrile infections of the upper respiratory tract. We then compared the results found in the young infants kept in the room disinfected by ultraviolet rays with the results found in the children aged 2 to 14 months, and kept in the four rooms on the ground floor.

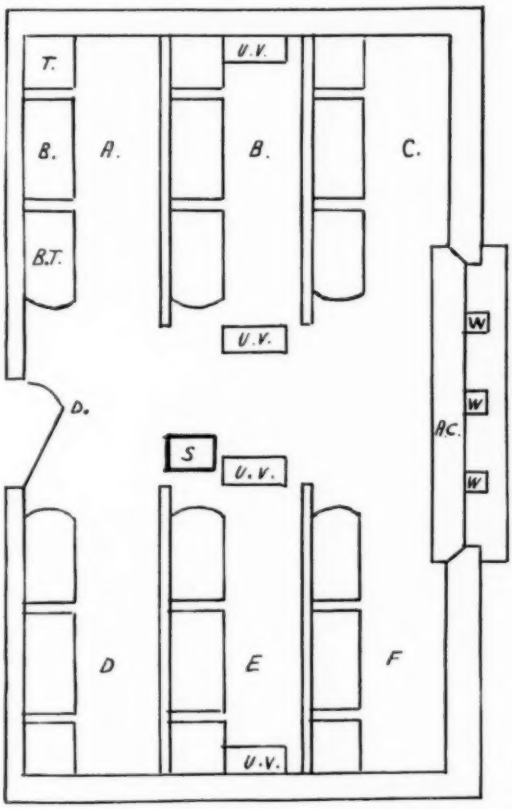

Fig. 1.—Plan of the room at the Clinique des Nourissons de Pinchat. *A.C.*, Air-conditioned; *B.T.*, bathtub; *W*, window; *B*, bed; *S*, sink; *T*, table; *U.V.*, ultraviolet ray lamp; *D*, door.

*We use Philips' 15 watt lamps.

†We use Merfen which has always been found satisfactory.

Results.—

Noxious Effect of the Ultraviolet Rays: We have never found that the ultraviolet rays exercised an effect detrimental to the health and development of the infants. No case of erythema or conjunctivitis has appeared in the children kept at a minimum of 1½ meters from the lamps.

a basis for comparison is on the average 5.53 per cent for 18,000 days present at the nursery. In the room disinfected with ultraviolet rays, the average of nasopharyngeal infections is 0.06 per cent. Out of 10,779 days we found a nasopharyngitis only four times and, in each case, it lasted hardly more than two days.

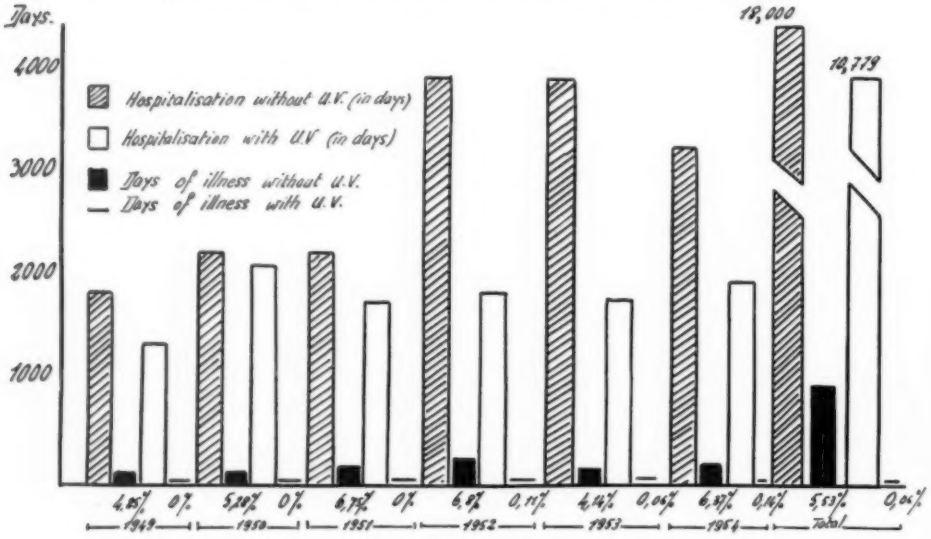

Fig. 2.—Respiratory tract infections at the Clinique des Nourissons.

TABLE I. RESPIRATORY TRACT INFECTION AT THE CLINIQUE DES NOURISSONS

	1949	1950	1951	1952	1953	1954	TOTAL
			I. *Comparison Standard*				
Days present	1,844	2,304	2,332	4,012	4,033	3,385	18,000
Days of illness	89	123	157	244	167	215	995
Percentage	4.85	5.28	6.75	6.08	4.14	6.37	5.53
			II. *Rooms With Ultraviolet Rays*				
Days present	1,420	1,800	1,782	1,867	1,785	2,125	10,779
Days of illness	0	0	0	2	1	3	6
Percentage	0	0	0	0.11	0.06	0.14	0.066

Among the personnel, one nurse came down with conjunctivitis and later had to wear dark glasses.

Protective Effect Against Infections: As Table I and Fig. 2 indicate, the proportion of upper respiratory infections in children taken as

The following incident demonstrates the efficiency of the ultraviolet rays. Jean, Jacques, and Pauline entered the Clinique des Nourrissons as soon as they left the Maternity Hospital. They stayed in the ultraviolet ray room during the

months of December, January, and February, remaining free from upper respiratory infections. In the beginning of March they were transferred to a room on the ground floor and therefore without ultraviolet rays. They were the only children in this particular room and were cared for by the same nurse as before. During this time there was a small epidemic of coryza in the nursery. One week after his transfer Jacques had a fever accompanied by a nasopharyngitis; two days later Jean and one day later Pauline came down with the same affection.

Discussion.—Although the system of nurseries existed for a number of years, the methods aimed at avoiding infections between children are of recent application.[25, 41] At the beginning of our century, transmissible diseases wreaked havoc. In 1900 the mortality in nurseries of the Paris region was 30 to 40 per cent.[9, 41] However, the separation of beds by partitions or complete separation by stalls brought the mortality down to lower than 10 per cent.[9, 21, 24, 33, 41] Finally, disinfection of objects meant for the infants, washing of hands,[31] the tracking down of germ carriers,[25] the wearing of a mask,[25] uniform and hat and disinfection of the rooms[12, 25, 27, 28, 30] and surrounding air[29, 38, 39, 43-46, 48, 49] not only lowered mortality but notably decreased morbidity.

Different methods of disinfection of the air have been proposed:

1. *The periodic or continuous pulverization of bactericidal substances* by means of aerosol, irritating neither the respiratory tract nor the mucosae of the patients and the personnel (triethylene-glycol, propylene-glycol, etc.).[3, 13-17, 19, 23, 35, 37, 38] The principle of the action of the aerosols resides in the fact that the bactericidal substances are particularly active when dispersed as very small droplets, the contact surface thus being as large as possible.

2. *Irradiation with ultraviolet rays.* Tubes electively emitting rays of a wave length of 2,537 Angstrom units are used.[22] According to Voogd and Daams[47] these waves are absorbed by the nucleoproteins of the microorganisms, thus preventing division and reproduction. Due to a protecting screen which directs the rays exclusively toward the ceiling, germicidal lamps can be used without any danger.

The first application of ultraviolet rays in a children's hospital goes back to 1936.[50, 51] Since 1939, their application has become general in the United States.[2, 6, 12, 18, 20, 22, 25, 30, 36, 40, 42, 43] So far as we know their appearance in Europe dates from after the World War II in Switzerland, Tobler [44-46] and Meyer[29] put them to good use in their service for premature infants.

In practice, disinfection of the air by ultraviolet rays is especially effective in the fight against respiratory tract infections.[1, 10-12, 17, 25, 30, 32, 42, 48, 49, 52] Our results correspond to those of Del Mundo[30] who found a 12.5 per cent frequency of respiratory tract infections in children kept in compartments without doors and only 2.7 per cent in the same compartments but including a barrier of ultraviolet rays at each entrance. Sauer[42] and Rosenstern[39] also observed twenty-one cases of respiratory tract infections due to contact in children kept in ordinary compart-

ments and only one case in children occupying compartments equipped with ultraviolet rays. Tobler[46] and Meyer[29] succeeded in eliminating plasma cell interstitial pneumonia from their premature ward due to the use of ultraviolet ray lamps.

stalled in our ward for premature babies, we have performed several experiments.

(1) *Action of the ultraviolet rays on the surrounding flora.*—Petri dishes, left open, were placed in each compartment, 1 meter from the floor,

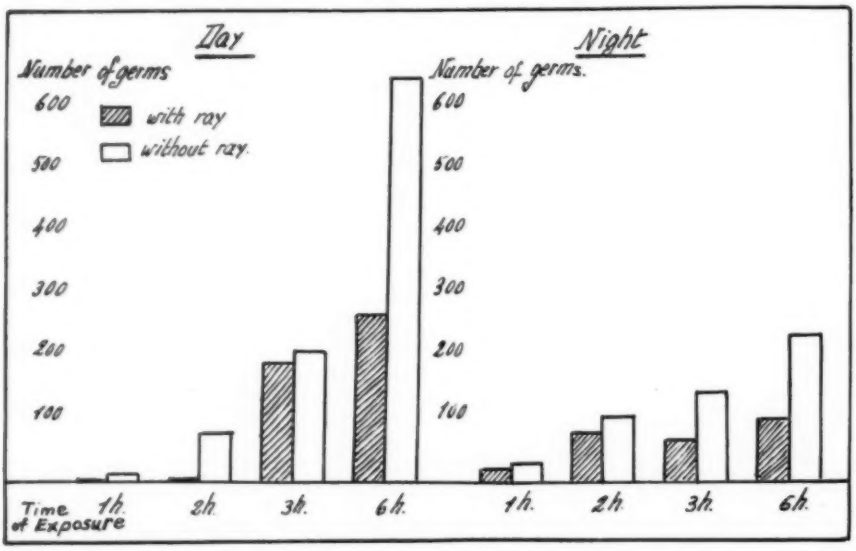

Fig. 3.—Effect of ultraviolet rays on the surrounding flora.

TABLE II. EFFECT OF ULTRAVIOLET RAYS ON THE SURROUNDING FLORA

TIME OF EXPOSURE OF THE PETRI DISHES	WITH RAYS			WITHOUT RAYS		
	TOTAL NUMBER OF GERMS	MOLDS	BACTERIA	TOTAL NUMBER OF GERMS	MOLDS	BACTERIA
			Daytime			
1 hr.	22	14	8	53	26	27
2 hr.	31	25	6	118	41	77
3 hr.	210	26	194	227	23	204
6 hr.	322	51	271	679	31	648
			At Night			
1 hr.	34	21	13	28	7	21
2 hr.	118	43	75	110	8	102
3 hr.	109	37	62	161	22	139
6 hr.	145	51	94	248	20	228

Study of the Bactericidal Power of Ultraviolet Ray Lamps.—In order to test the bactericidal power of ultraviolet ray lamps such as we have in-

near the bed of the child. A first group was left open for 1 hour, a second for 2 hours, a third for 3 hours, and a fourth for 6 hours. One

experiment was done during the day when the nurses were on full duty, and a second at night. For comparative purposes the dishes were exposed without ultraviolet ray lamps being turned on, and with the lamps turned on.

Results: The results are summarized in Table II and Fig. 3. When the air was not disinfected by ultraviolet rays, the number of bacteria or molds which fell into a Petri dish in one daytime hour was 53 on the average (maximum 72, minimum 37). On the other hand, the average was 23 (maximum 30, minimum 18) if the ultraviolet ray lamps were lit. If we allow for the fact that molds are not sensitive or only slightly sensitive to ultraviolet rays, we arrive at the ratio of 5 germs to 15 in the comparison experiment, or one-third.

To show the different sources of variations of the effectiveness of the ultraviolet rays on the surrounding flora, we analyzed the variant considering three sources of variations:

(a) Source A which represents the number of hours during which the Petri dishes were opened (1 hr., 2 hr., 3 hr., 6 hr.);

(b) Source B representing the time of day the experiments were done (day or night);

(c) Source C the experiment performed with ultraviolet rays and the comparison standard without ultraviolet rays.

The interpretation of the results, summarized in Table III, follows:

(a) The differences observed in the number of bacteria counted in the Petri dishes left open 1, 2, 3, or 6 hours are very significant. Therefore the duration of exposure of the Petri dishes is not indifferent and, as Table II distinctly demonstrates, the best duration of exposure is between 2 and 3 hours.

TABLE III

SOURCES OF VARIATIONS	SUM OF SQUARES	DEGREES OF FREEDOM	AVERAGE OF SQUARES	F	
A	1,169,007.71	3	389,669.24	58,484	TS
B	165,507.04	1	165,507.04	24,840	TS
C	189,748.17	1	189,748.17	28,478	TS
AB	409,809.20	3	136,603.07	20,502	TS
AC	215,937.56	3	71,979.19	16,803	TS
BC	21,236.50	1	21,236.50	3,187	NS
ABC	63,315.28	3	21,105.09	3,168	S
Within	533,029.50	80	6,662.87		
Total	2,234,561.46	95			

The difference is still more manifest after 2 hours of exposure. After elimination of the molds, the number of germs in the room when treated with ultraviolet rays is one-twelfth the number of germs in the room when not treated with ultraviolet rays. At the end of 3 hours of exposure, there is no significant difference, but at the end of 6 hours there is a distinct difference.

(b) The differences found between the observations made at night and those done in the daytime (variation B) are likewise significant. According to Table II, it seems that the bactericidal action of the ultraviolet rays is stronger during the day, when

there is more movement in the room, than during the night. Undoubtedly, during the night the air circulates less and passes in front of the rays only in small portions, which definitely diminishes the bactericidal effect of rays on the surrounding air.

(c) The bactericidal effect of the ultraviolet rays on the surrounding air is manifest. Here again there is a significant difference between the number of bacteria found on the Petri dishes while the ultraviolet ray lamps are on and the number found while the lamps are off (variation C).

Immediately after the end of the vaporization, a first group of 6 dishes was exposed for 5 minutes; one hour later, a second group was exposed for 15 minutes; 4 hours later a third group; 8 hours later, a fourth and last group. For comparison the same experiment was performed in the room which was not irradiated. Finally, since the bactericidal effect of the ultraviolet rays is very rapid, a second experiment was made, during which the Petri dishes were opened every 15 minutes.

TABLE IV. ACTION OF THE ULTRAVIOLET RAYS ON BACTERIUM PRODIGIOSUM PULVERIZED IN LARGE AMOUNTS IN THE ROOM

	COMPARISON STANDARD		WITHOUT ULTRAVIOLET RAYS COMPARTMENTS						AVERAGE AFTER 15 MINUTES OF EXPOSURE
	TIME BETWEEN VAPORIZATION AND REMOVAL OF SPECIMEN	EXPOSURE TIME (MIN.)	A	B	C	D	E	F	
I	5 min.	5	2,500	1,840	2,560	3,200	3,220	3,741	8,531
II	1 hr.	15	1,380	1,550	1,200	1,360	1,300	1,080	1,315
III	4 hr.	15	33	35	22	26	31	34	30
IV	8 hr.	15	22	18	9	6	7	17	13
		of which	0 p	1 p	10 p	0 p	1 p	1 p	2 p

p = *Bact. prodigiosum*

TABLE V. WITH ULTRAVIOLET RAYS

	TIME BETWEEN VAPORIZATION AND REMOVAL OF SPECIMEN	EXPOSURE TIME (MIN.)	COMPARTMENTS						AVERAGE AFTER 15 MINUTES OF EXPOSURE
			A	B	C	D	E	F	
I	5 min.	5	4,370	4,300	3,200	3,664	3,264	3,712	11,255
II	1 hr.	15	3 p + 4	0 p + 5	2 p + 4	13 p + 3	1 p + 6	3 p + 1	3 p + 4
III	4 hr.	15	8 p + 1	4 p + 2	0 p + 1	0 p + 5	0 p + 0	0 p + 8	2 p + 3
IV	8 hr.	15	0 p + 2	0 p + 7	0 p + 6	0 p + 3	0 p + 1	0 p + 6	0 p + 4

(2) *Action of the ultraviolet rays on the microbes pulverized in large quantities in the room.*—A suspension of *Bacterium prodigiosum (Serratia marcescens)*, cultured for twenty-four hours in broth, was vaporized in each compartment with three complete pushes on the piston handle of a "Flytox" vaporizer. On each bed was placed a Petri dish containing gelose.

Results: As shown in Tables IV, V, and VI, as well as in Fig. 4, one hour after the vaporization with the *Bact. prodigiosum*, their number in the air is still high. However, after 4 hours, there was a great reduction in their number, undoubtedly because microorganisms settle toward the ground.

With ultraviolet rays, the number of *Bact. prodigiosum* diminishes rap-

TABLE VI. WITH ULTRAVIOLET RAYS

TIME BETWEEN VAPORIZATION AND REMOVAL OF SPECIMEN	EXPOSURE TIME (MIN.	COMPARTMENTS A	B	C	D	E	F	AVERAGE AFTER 15 MIN. OF EXPOSURE
I Before pulver.	5	7	9	0	[illegible]	8	0	
II Immed.	5	5,470	5,250	5 170	5,612	5,736	5,280	16,260
III 15 min.	5	46 p + 2	71 p + 2	68 p + 2	61 p + 3	68 p + 1	51 p + 6	184 p + 8
IV 30 min.	5	5 p + 2	7 p + 6	3 p + 6	4 p + 10	0 p + 3	1 p + 3	10 p + 8
V 45 min.	5	0 p + 1	4 p + 14	3 p + 15	0 p + 15	0 p + 3	1 p + 3	4 p + 25

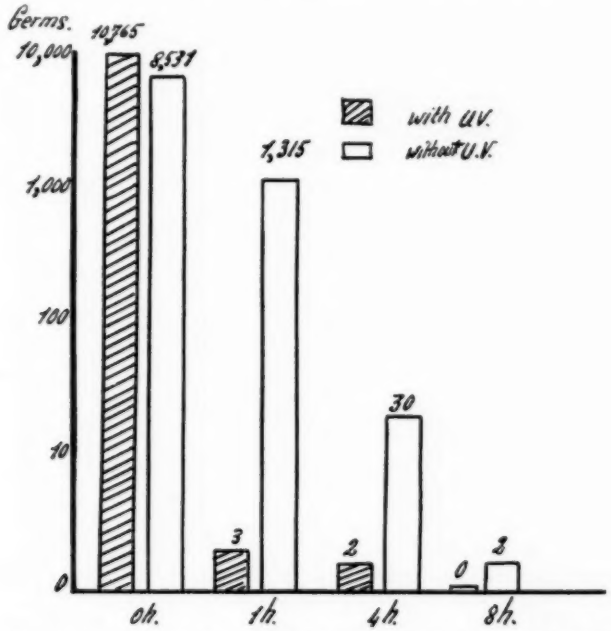

Fig. 4.—Destruction of *Bact. prodigiosum* by the ultraviolet rays. Semilogarithmic scale.

idly, after 15 minutes there is a decrease from 16,260 to 192. In one hour, without ultraviolet rays the number is diminished from 8,530 to 1,315. These figures indicate clearly the bactericidal action of ultraviolet rays on microbes vaporized into a room in large amounts.

(3) *Blocking effect of the lamps placed at the entrance of the compartments.*—In order to study the passage of germs from one compartment to another and the screening effect of the lamps, we vaporized *Bact. prodigiosum* (24-hour broth culture) into a compartment (compartment C, Fig. 1). We then counted the number of colonies which appeared in the Petri dishes placed in the different compartments.

Results: If ultraviolet rays are not used, there is a rapid contamination of the neighboring compartment; 15 minutes after the vaporization the same number of germs are found in all the compartments (Table

VII, *A*). If the lamps remain lighted they do not prevent the passage of the bacilli from one compartment to another; as the bacilli penetrate either through the corridor or above the walls separating the compartments (Table VII, *B*). On the other hand, the bactericidal action of the ultraviolet rays is manifest, since, 15 minutes after the vaporization, only 23 to 115 germs are found per compartment, whereas there are more than 1,000 per compartment in the group used as a comparison.

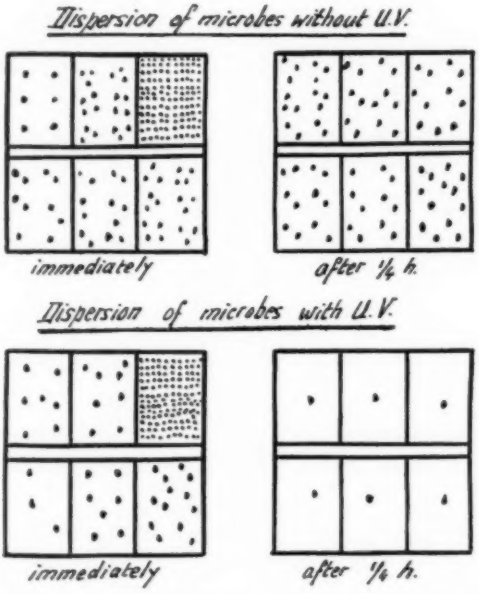

Fig. 5.—Blocking effect of ultraviolet rays and dispersion of microbes without ultraviolet rays.

TABLE VII. DETERMINATION OF THE NUMBER OF GERMS IN EACH COMPARTMENT AFTER EXPERIMENTAL INFECTION OF COMPARTMENT BY PULVERIZATION WITH BACT. PRODIGIOSUM

IMMEDIATELY			AFTER 15 MIN.			AFTER 30 MIN.			AFTER 45 MIN.		
A. Comparison standard, without ultraviolet rays											
A	B	C	A	B	C	A	B	C	A	B	451
679	2,006	10,840	1,641	1,380	1,163	836	826	791	458	402	452
1,098	1,310	2,019	1,253	1,134	1,362	629	813	728	366	463	
D	E	F	D	E	F	D	E	F	D	E	C
B. With protection by ultraviolet rays											
A	B	C	A	B	C	A	B	C	A	B	C
13,100	842	710	115	78	88	17	6	11	18	8	0 p
						9 p	2 p	7 p	0 p	1 p	3 g
						12 g	4 g	3 g	8 g	4 g	0 m
						6 m	0 m	0 m	0 m	3 m	5
385	719	1,370	23	32	82	7	9	20	10	10	1 p
						2 p 2	2 p	5 p	3 p	0 p	2 g
D	E	F	D	E	F	5 g	7 g	2 g	3 g	6 g	2 m
						0 m	0 m	3 m	4 m	4 m	3
						D	E	F	D	E	F

p, prodigiosum; g, other germs; m, molds.

DISCUSSION

As our experiments have demonstrated, it seems that the ultraviolet rays have no action on the surrounding flora while the infants are sleeping. However, the number of germs which increases during the daytime care of the child is diminished by the ultraviolet rays. Hamburger and his collaborators[13, 14] came to similar results by using vapors of triethyleneglycol as a disinfectant; however, they were also able to further diminish the surrounding flora (beta-hemolytic streptococci in particular) by treating the bedding and sheets of the patients with a disinfectant and by applying a disinfecting solution on the floor.

During massive infection in a compartment, the blocking effect of the lamps, as we placed them, is definitely insufficient. On the other hand, there is a distinct bactericidal effect since the number of germs diminish rapidly. This is important since, if an infant comes down accidentally with a respiratory tract infection, he will in all probability be the only one infected as the germs that he will sneeze or breathe into the air will be rapidly destroyed by the ultraviolet rays.

CONCLUSIONS

In the Clinique des Nourrissons of Geneva where we hospitalize children with contagious diseases, premature infants, and healthy boarders, we have been able to avoid epidemics of contagious diseases for a period of six years by an isolation system. On the other hand, respiratory, throat, and ear infections and cases of submaxillary adenitis have not been eliminated. During six years, we have had 995 days of sickness out of 18,000 days present.

In a ward for premature or newborn children and feeble infants of less than 3 months of age, we have been able to eliminate respiratory infections almost completely by humidification of the air, and its disinfection by ultraviolet rays. We have had 6 days of disease out of 10,779 days present.

A study of the bactericidal effect of ultraviolet rays has demonstrated that they probably do not act by forming a protective screen in the installation, but rather by rapidly destroying the bacteria which circulate in their field of action.

Since we have never observed the slightest noxious action of the quartz lamps on our children, we suggest and recommend the disinfection with ultraviolet rays of rooms for premature and feeble babies who are especially sensitive to respiratory tract infections. Our unit including six compartments, separated by glass walls which do not reach the ceiling and which open into the same corridor, has given us complete satisfaction as long as the air is humidified at 50 per cent and disinfected by ultraviolet rays.

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THE EFFECT OF SIMULATED EXCHANGE TRANSFUSION IN PUPPIES

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EXCHANGE transfusion is an established therapeutic technique for the treatment of erythroblastosis fetalis. Since the methods of treatment have become more or less standardized the rate of deaths among treated infants has not varied appreciably in our series of infants, or those of others.

The severity of the hemolytic process, the presence of edema and of shock, the influence of prematurity, and of narcosis on the infant are factors usually beyond the control of the exchange transfusion team. Ionic imbalance, exposure, undue handling, and the speed of the exchange of blood, however, are the team's immediate responsibility. Calcium can be replaced, and the infant can be given oxygen and protection. However, the time consumed in the procedure is determined primarily by the clinical judgment of the operator.

A consensus of the current literature indicates that most exchange transfusions are accomplished in one to two hours.[1-7] These "optional" times are based on clinical experience. Specific warnings against rapid procedures, especially in small or severely ill patients, appear.[7, 8]

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Since normal laboratory animals and human beings seem to adjust to acute, small alterations of blood volume quite easily, it was difficult for us to accept either speed or volume alone as a factor causing deaths in exchange transfusion.

A simple experiment was performed in which healthy young puppies were subjected to one- and two-vessel techniques of simulated replacement transfusions using their own heparinized blood, varying their total blood volume, at the usual rates and volumes, and at rates and volumes far in excess of those ordinarily used in newborn infants.

MATERIALS AND METHODS (TABLE I)

Healthy young mongrel puppies from 1,500 to 3,000 grams were lightly anesthetized with Nembutal and heparinized. A jugular vein was exposed and cannulated. A carotid artery was exposed and cannulated. The contralateral femoral artery and vein were prepared for injection and withdrawal of blood, using polyethylene catheters.

Simultaneous pressures were recorded from the jugular vein and carotid artery, and the electrocardiogram was recorded, using Sanborn electromanometers and the "Poly-Viso" 4-channel recorder.

TABLE I

DOG		PRESSURE IN MM. HG.								EKG	TOTAL C.C. "EXCHANGED"	TIME (MIN.)	PROCEDURE
		CONTROL I		MAXIMUM		MINIMUM		CONTROL II					
		A	SVC	A	SVC	A	SVC	A	SVC				
													1 Vessel
I	a	115/95	5/3	115/95	5/3	115/95	5/3	115/95	5/3	No change	30	1	5 c.c. in 5 c.c. out
	b	115/95	5/3	125/100	7/4	110/95	4/2	120/100	10/2	No change	50	1	10 c.c. in 10 c.c. out
	c	115/90	5/3	140/110	Mean 10	90/75	Mean 5	100/85	5/3	No change	100	1	20 c.c. in 20 c.c. out
	d	100/85	5/3	100/90	17/10	40/30	4/3	115/95	5/3	Transient T inversion	220	2	40 c.c. in 40 c.c. out
II	a	85/60	9/7	100/75	10/8	80/60	9/7	100/70	12/10	No change	100	3	10 c.c. in 10 c.c. out
	b	100/70	12/10	120/80	20/10	95/60	12/9	90/70	18/10	No change	100	3	20 c.c. in 20 c.c. out
	c	90/70	18/10	75/45	38/14	50/40	16/8	72/50	17/10	Transient Peaked T	300	5	30 c.c. in 30 c.c. out
	d	72/50	17/10	85/50	8/7	85/58	8/7	85/60	8/7	No change	300	15	Simultan. 2 vessels
III	a	95/60	3/1	85/50	Mean 2	70/35	Mean 2	95/60	3/1	No change	75	2	15 c.c. in 15 c.c. out
	b	95/60	3/1	70/35	3/1	Shock and Death					120	2	Excessive Nembutal 30 c.c. in 30 c.c. out
IV	a	85/68	4/0	80/60	14/10	60/50	4/0	70/58	4/2	No change	400	4	50 c.c. in 50 c.c. out
	b	70/58	4/2	Rapid of	Bleeding 160 c.c.	10/5	2/0						
	c	10/5	2/0	38/20	4/2	20/12	2/0	58/40	2/0	No change	270	3	30 c.c. in 30 c.c. out
	d	58/40	2/0	60/38	2/0	20/18	2/0	70/50	5/0	No change	400	3	50 c.c. in 50 c.c. out
	e	70/50	5/0	70/52	7/3	20/15	1/0	70/65	1/0	No change	300	3	100 c.c. in 100 c.c. out
	f	70/65	1/0	180 c.c. Blood & Saline Reinjected				76/55	1/0	No change			
V	a	90/70	9/6	100/85	9/6	100/85	9/6	100/85	11/8	No change	365	3	Simultan. 2 vessels
	b	100/85	11/8	100/80	9/6	90/78	9/6	98/80	9/6	No change	750	4	125 c.c. in 125 c.c. out 1 Vessel

A, Carotid artery; SVC, superior vena cava.

A, Carotid artery; SVC, superior vena cava.

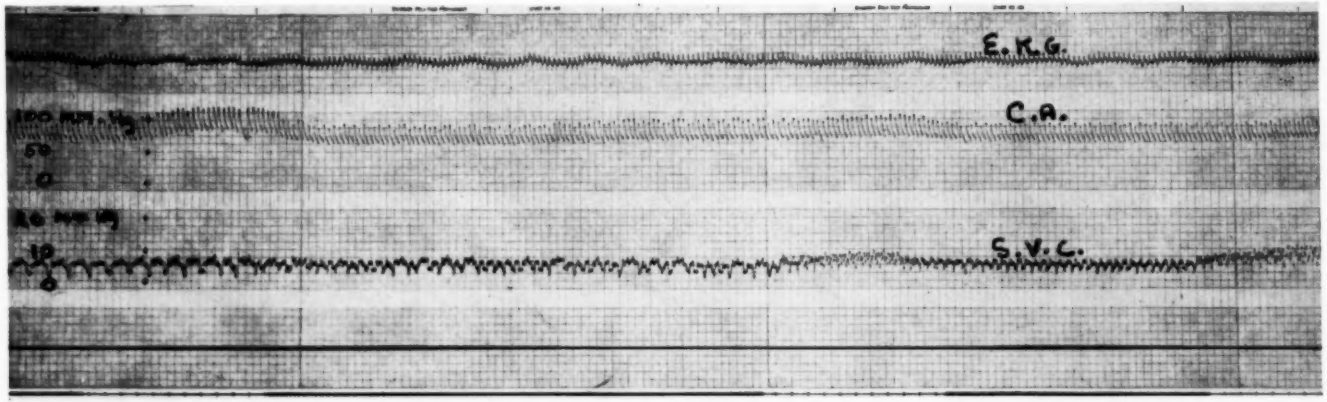

Fig. 1.—Dog's weight 3,000 grams. Recorded before dog was given excessive dose of Nembutal. Injections and withdrawals of 30 c.c. volumes, five times per 2½ minutes. A slight elevation of arterial pressure occurs during injection. Venous pressure is unaltered. Over-all effects are minimal. *E.K.G.*, Electrocardiogram; *C.A.*, carotid artery pressure; *S.V.A.*, superior vena caval pressure.

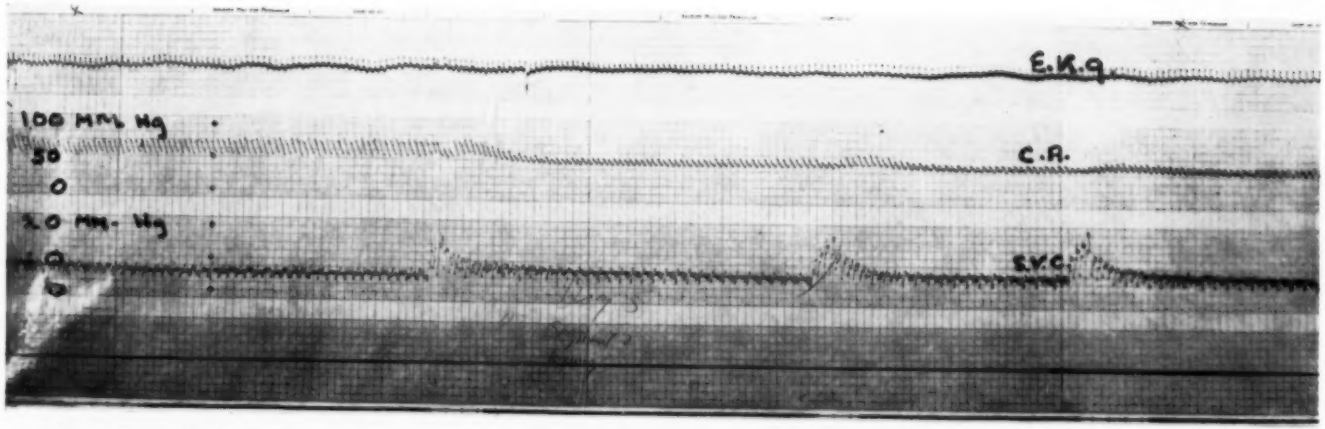

Fig. 2.—Same dog as in Fig. 1. After excessive narcotization. Arterial pressure is falling during procedure; pulse pressure is becoming smaller. Wide oscillations of venous pressure occur during injection. Procedure same as Fig. 1. (Injections and withdrawals of 30 c.c. volumes.) *E.K.G.*, Electrocardiogram; *C.A.*, carotid artery pressure; *S.V.C.*, superior vena caval pressure.

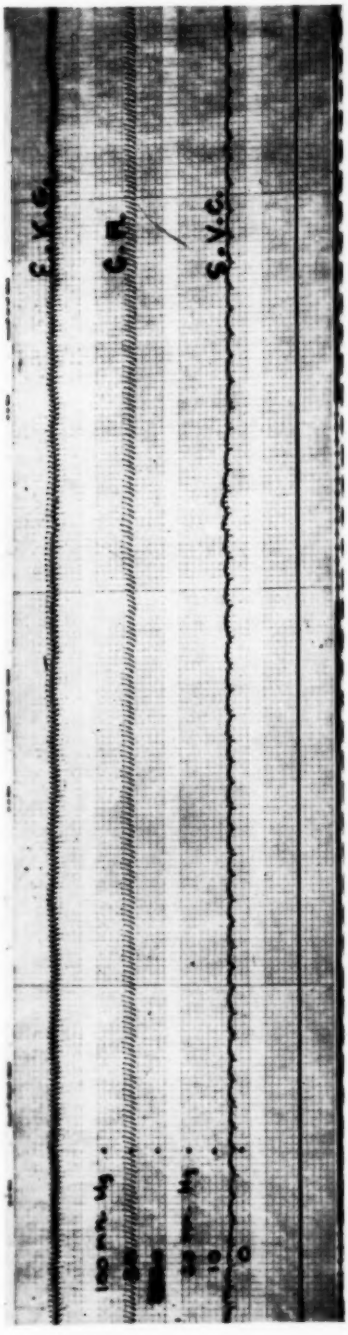

Fig. 3.—Recorded during simultaneous injection and withdrawal of 365 c.c. of blood in 5 minutes. Dog's weight 2,040 grams. *E.K.G.*, Electrocardiogram; *C.A.*, carotid artery pressure; *S.V.C.*, superior vena caval pressure.

Dog 1, weight 1,560 grams.—Using a femoral vein only, increasing volumes of blood from 5 to 40 c.c. were injected and withdrawn at a rapid rate, so that totals of 30 to 220 c.c. were injected and withdrawn in intervals under 3 minutes. The control recordings showed no significant change in arterial or venous pressures, except that a transient fall in arterial pressure and transient T-wave inversion occurred during withdrawal of the 40 c.c. portions. At the end of this procedure all recordings had returned to the control status.

Dog 2, weight 2,500 grams.—Single-vessel technique—exchange transfusion up to a maximum of 300 c.c. in 5½ minutes was given with no significant changes in recorded pressures and electrocardiogram. This procedure was then repeated, using two vessels with simultaneous injection and withdrawal. Again, the animal tolerated an exchange transfusion in excess of its total calculated blood volumes in ten minutes, with no changes in arterial or venous pressures.

Dog 3, weight 2,040 grams.—This puppy was subjected first to an exchange transfusion of 750 c.c. in 4½ minutes (one vessel used), followed by the simultaneous injection and withdrawal of 365 c.c. in 5 minutes (two-vessel technique). The changes in arterial and venous pressures and electrocardiogram were insignificant.

Dog 4, weight 2,400 grams.—The animal was first subjected to a 400 c.c. exchange transfusion in 4 minutes. There was very little change in the pressure recordings. The animal was now bled into shock by removing 160 c.c. of an approximate 240 c.c. blood volume, to the point where the arterial pressure was only 10/5. Using injection and withdrawal volumes of 30, 50, and finally 100 c.c., three replacement transfusions of 300 to 400 c.c. each in approximately 3 minutes were successively performed. Wide osscillation in the arterial blood pressure was noted, from 20/15 during withdrawal of blood up to 70/50 during injection. Following these three procedures the arterial and venous pressures were approximately the same as those recorded before bleeding the animal. At the close of the final control recordings 160 c.c. of blood was administered to the animal. The final pressures were approximately the same as those recorded at the start of the experiment.

Dog 5, weight 3,000 grams.—Injection and withdrawal of 30 c.c. volumes, five times in 2¼ minutes were done with no effect on arterial or venous pressure. The animal was then heavily narcotized with an overdose of Nembutal. The arterial pressure fell from 95/60 and stabilized at 70/35. Then 30 c.c. injections and withdrawals were repeated, and after 120 c.c. had been withdrawn and injected in a 2-minute period, the animal's arterial pressure began to fall rapidly, and despite intravenous fluids and oxygen the animal went into a state of shock and died.

DISCUSSION

The above data demonstrate that in normal young puppies simulated exchange transfusions by one-vessel techniques may be safely accomplished, using larger aliquots and more rapid rates of exchange than we had anticipated.

The vascular trees of puppies were expanded and contracted by as much as 25 per cent of their calculated blood volume without significantly altering venous or arterial pressures. Neither

did the electrocardiographic tracings show significant aberrations.

The maintenance of cardiovascular homeostasis in healthy young puppies under challenges far exceeding those that ordinarily occur during routine replacement transfusion of newborn infants might well be expected; particularly if one considers the elasticity of the puppies' venous systems, and the ability of their hearts to adapt to varying work.

One puppy (No 5) was given an excessive amount of Nembutal, depressing markedly his reflex activity. When this puppy's cardiovascular system was challenged in a manner similar to the other puppies, the arterial pressure fell sharply, and the venous pressure rose significantly.

Shock was produced in another puppy (No. 4) by rapidly withdrawing 66 per cent of his estimated blood volume. When this puppy's remaining blood volume was rapidly increased and decreased, wide oscillations of the pulse pressure appeared transiently.

The situations outlined might indicate that noxious stimuli (e.g., narcosis and shock) may upset homeostatic mechanisms present in normal, lightly anesthetized and heparinized puppies.

Whereas healthy puppies may tolerate the dynamic changes consequent to a rapid one-vessel exchange transfusion, puppies subjected to noxious stimuli may not be able to cope with this added burden.

These animal experiments corroborate the clinical experiences acquired during the care of more than 300 erythroblastotic infants.

While we have accomplished 500 c.c. exchange transfusions on erythroblastotic premature infants in less than 40 minutes, we have also needed several hours to accomplish the same procedure in much larger and more mature infants.

Size of the infant, prematurity, and laboratory evidence of erythroblastosis fetalis have not caused us to decrease either the rate or volume of transfusion.

The rates, aliquots, and total volume of blood we have used in transfusing erythroblastotic infants have always been guided by a continuous appraisal of their general condition. In particular, we have been guided by cardiac rate and rhythm, by respiratory rate, and by venous pressure at the umbilical vein. Whenever the cardiac rate, respiratory rate, or venous pressure began to climb, we have felt that the procedure was affecting the infant adversely. In such a situation the transfusion was either slowed or discontinued until there was evidence that homeostasis was restored.

We have learned that no one rate or volume of transfusion is applicable to all infants. We feel that each infant should have his exchange transfusion accomplished at as rapid or slow a rate as is proper to maintain his homeostatic rate.

No infant should be transfused slower than need be for this prolongs his stay away from a controlled and protected environment. Contrariwise, no infant should be endangered by too rapid and too large transfusions. The clock has no place in the transfusion routine of erythroblastotic infants. A replacement transfusion must proceed either as fast or as slowly as is consistent with maximum safety for the infant. The more critically ill the infant, the more precautions will be

needed. These may well include a very slow rate and small aliquots, or a two-vessel technique of transfusion.

CONCLUSIONS

1. The rates at which a simulated exchange transfusion may be accomplished, and the aliquots which may be used in normal puppies lightly anesthetized with Nembutal and heparinized, are greater than anticipated.

2. The two-vessel replacement transfusion techniques may produce less effect on arterial and venous blood pressures than the ordinary one-vessel technique.

3. Shock or narcosis may decrease a puppy's ability to adjust to the stimulus of alternately expanding and contracting the blood vascular tree.

4. We wish to emphasize that this study of young puppies was only concerned with speed of transfusion and the volume of blood related to that rate. We do not advocate such rapid rates or large volumes for exchange transfusions in newborn infants with erythroblastosis.

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The quiet manner and the gentle voice which all who have been ill know how to value in their attendants, are especially needed when the patient is a child. Your first object must be not to alarm it; if you succeed in avoiding this danger, it will not be long before you acquire its confidence. Do not, therefore, on entering the room, go at once close up to the child; but, sitting down sufficiently near to watch it, and yet so far off as not to attract its attention, put a few questions to its attendant. While doing this, you may, without seeming to notice it, acquire a great deal of important information; you may observe the expression of the face, the nature of the respiration, whether slow or frequent, regular or unequal; and if the child utters any sound you may attend to the character of its cry. All your observations must be made without staring the child in the face; little children, especially if ill, seem always disturbed by this, and will be almost sure to cry.

CHARLES WEST: LECTURES ON CHILDREN.

RELATIONSHIP OF RETROLENTAL FIBROPLASIA TO OXYGEN CONCENTRATION

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THE relationship between retrolental fibroplasia and the prolonged exposure of oxygen has been recently demonstrated. Szewczyk[1] suggested that anoxia may have some relation to its development. Others have pointed out that retrolental fibroplasia has appeared only since specialized care, including prolonged oxygen administration, has been provided for hospitalized premature infants.[2] In 1952, Patz and associates[5] presented evidence that the development of the cicatricial phases of retrolental fibroplasia may be related to prolonged use of high concentrations of oxygen. Lanman and coworkers[6] substantiated this in May, 1954.

The purpose of the present report is to present further evidence that in the premature infant retinal detachment, whether partial or complete due to retrolental fibroplasia, is in some way related to the prolonged use of high concentrations of oxygen. When the use of oxygen was sharply restricted in the Premature Unit of the Children's Hospital, the incidence of cicatricial retrolental fibroplasia became negligible. When this investigation was started, only one controlled study had been reported. At that time, the use of liberal quantities of oxygen, and in most instances without regard to concentration, was standard practice in most premature nurseries in the United States. It was decided to attempt a controlled experiment in which observations were systematically made on the effect of alteration in only one variable, oxygen concentration, upon the incidence of retrolental fibroplasia.

PLAN OF STUDY

This study began July 1, 1952, and terminated June 30, 1953. The premature infants in the study were divided into two groups upon admission to the Premature Center on an alternate case basis. One group was maintained in an oxygen concentration of 60 to 64 per cent for thirty days, while the other group remained in a concentration of 30 per cent for thirty days. All infants observed were housed in incubators.* Oxygen was administered from an outside bank of tanks and was supplied to the incubator from a wall source. Oxygen concentrations in each incubator were determined every three hours for the duration of the study, using an oxygen analyzer.†

All infants were fed gradually increasing amounts of milk, so that by

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The oxygen used in this study was in part made available through the generosity of the Linde Air Products Company.

*Incubators used were Chappel Isolette and Gordon-Armstrong.

†Oxygen analyzer used was an OEM analyzer.

the end of the eighth or tenth day of life, they were receiving 125 cal. per kilogram per day of an artificial milk mixture containing 20 per cent of the calories as protein, 64 per cent as carbohydrate, and 16 per cent as fat. A water-miscible preparation of vitamin supplement was started on the eighth day of life; this supplied 5,000 I.U. vitamin A, 1,000 I.U. vitamin D, and 50 mg. vitamin C each day. Parenteral vitamin K was not administered.

The infants in the study ranged in weight, at birth, from 1,075 to 2,000 grams. Any infant on admission who appeared seriously ill with severe respiratory distress or any other condition that gave a guarded prognosis for life was not included in the study. A total of eighty-three infants was observed. The final ophthalmologic examination was recorded between six and ten months after birth. Eye examination was started between the second and third week after birth and continued at weekly intervals thereafter until discharge from the nursery at a weight of 2,500 grams. After discharge, ocular examination was performed at monthly or more frequent intervals in infants who showed fundus changes at the time of discharge. This frequency of examination was continued until the fundi stabilized. The examination was performed by two observers: one an ophthalmologist and one a pediatrician who had been working as a team for a period of four years. A finding was not recorded until there was complete agreement on the observation. The pupils were dilated by instilling 2 drops of 10 per cent Neo-Synephrine hydrochloride and 2 drops of 1 per cent homatropine hydrobromide into both conjunctival sacs sixty and thirty minutes before visualization. The infant was secured in a blanket with only the head protruding and a rubber nipple with cotton soaked in 5 per cent lactose water was held in the infant's mouth. The infant was placed on a flat crib-side table and both observers took their turns, first as holder and then as observer. This simple technique allowed adequate fundus visualization. In only three instances was it necessary to employ a small lid speculum because of very narrow palpebral apertures. After the age of 6 months, however, it occasionally became necessary to perform the examination under general anesthesia. This was done to ensure complete visualization of the fundus in a squirming infant. The same anesthetic precautions were observed as for any infant given a general anesthetic.

RESULTS

The results are summarized in Table I. Classification of fundus changes is in accordance with the nomenclature adopted by a Subcommittee for the Classification of Retrolental Fibroplasia appointed by the National Society for the Prevention of Blindness.

The discrepancy between the number of infants in each group, despite the fact that the study began as an alternate case method, requires explanation. It was possible, through oversight of the admitting personnel, to admit two or more successive infants to the identical oxygen concentrations. Once an infant was placed in a given oxygen concentration, this concentration was maintained for thirty days.

It will be noted from Table I that 45 per cent of the total number of infants in the high oxygen group developed retinal vascular changes, 36 per cent partial cicatricial changes, and

16 per cent complete cicatricial changes or blindness; while 9 per cent of the infants in the low oxygen group developed retinal vascular changes, 3 per cent partial cicatricial changes, and none developed complete cicatricial changes. Furthermore, although not shown in the table, the one infant who developed partial retinal detachment in the low oxygen group subsequently showed ophthalmologic evidence of retinal reattachment. The final ophthalmologic examination (6 to 10 months after birth) revealed, in the high oxygen group, eight infants (16 per cent) with stage V retrolental fibroplasia and nine infants (18.3 per cent) with stage IV retrolental fibroplasia; this represents seventeen infants (36 per cent) with permanent visual visibility. All infants who originally developed stages I and II retrolental fibroplasia and did not advance further receded to normal at the time of the final examination; this reversal was also observed in the low oxygen group. The largest number of visual defects occurred in the smaller birth weight group. Both eyes were involved in an identical process in the affected infants.

TABLE I. EFFECT OF HIGH AND LOW CONCENTRATION OF OXYGEN IN INCUBATORS ON THE INCIDENCE OF RETROLENTAL FIBROPLASIA

OXYGEN CONCENTRATION	BIRTH WEIGHT	NO. OF INFANTS OBSERVED	STAGES OF RLF			
			NORMAL	I-II	III-IV	V
High	1,001-1,500	25	12	13	11	6
	1,501-2,000	24	15	9	6	2
Low	1,001-1,500	6	4	2	0	0
	1,501-2,000	28	27	1	1	0

DISCUSSION

The use of oxygen for the premature infant has been standard practice for many years.[7] This has increasingly been associated with the establishment of special centers for the care of premature infants[4] in the effort to reduce the high mortality of this group of infants. The administration of oxygen has, in most instances, been regulated only according to liter flow per minute. Little or no attempt has been made to measure or control oxygen in incubators. As pointed out by Szewczyk, and in our own experience, wide fluctuations in oxygen concentrations may occur over a twenty-four-hour period if one simply relies on liter flow alone; leaks in the incubator and tubing, rise or fall in pressure along the line of a piped-in supply, and several other errors all contribute to variation in concentration.

The data obtained appear to indicate that the incidence of permanent visual disturbance due to retrolental fibroplasia is related in some way to the prolonged use of high concentration of oxygen (60 to 64 per cent concentration). One cannot, however, deduce the mechanism of the change from these data. All infants at the end of thirty days were removed abruptly from their incubator oxygen concentration to ambient oxygen concentration and no attempt was made to wean them gradually; such a step would have added a new variable. We are not prepared, therefore, to deduce from our data that abrupt withdrawal effects the incidence of permanent visual defects from retrolental fibroplasia.

Following the termination of this study, the routine of oxygen admin-

istration in our Premature Center was completely revised. Oxygen in concentrations above that of outside air up to 38 per cent and enriched with moisture (aerosol) is being administered to infants who are cyanotic from respiratory distress only. These infants remain in this environment continuously for periods varying from twelve hours to seven days; usually, by that time, clinical evaluation indicating improved respiratory exchange allows for their abrupt removal to room air without obvious distress. During the period from Sept. 1, 1953, through Jan. 1, 1955, using this routine, we have observed no case of blindness. Table II lists, by birth weight, the results of ocular fundus examinations in the infants observed during this period. It will be noted that only one infant showed the early acute phase of RLF. This infant, because of serious respiratory distress which subsequently disappeared, remained for the first fifteen days of life in the oxygen aerosol-enriched atmosphere as previously outlined. At present, the ocular fundi are completely normal.

Table III lists differences in mortality rates of all infants admitted to the Premature Center, combining those born in the Maternity Division of Children's Hospital and those transported to the Premature Center from outside the Children's Hospital. These rates are listed for the period during the controlled oxygen study and for the more recent period of restricted oxygen therapy. It will be noted that during the latter period there was no increase in mortality rate; indeed, a slight reduction occurred in the two groups weighing less than 1,500 grams at birth. Incidentally, it was observed that there were fewer deaths due to hyaline membrane disease among premature infants during the "restricted oxygen" year than during the period when large amounts of oxygen were being used. This will be the subject of a subsequent report.

TABLE II. EFFECT OF RESTRICTED USE OF OXYGEN ON THE INCIDENCE OF RETROLENTAL FIBROPLASIA

BIRTH WEIGHT (GRAMS)	NO. OF INFANTS OBSERVED	NO. OF INFANTS WITH NORMAL FUNDI	STAGES OF RLF	
			I-II	V
1,001-1,500	28	27	1	0
1,501-2,000	77	77	0	0

TABLE III. MORTALITY RATES DURING OBSERVATION PERIODS

BIRTH WEIGHT (GRAMS)	1952-53 (CONTROLLED O_2 STUDY)			1954 (RESTRICTED OXYGEN)		
	NO. SURVIVED	NO. DIED	MORTALITY RATE (%)	NO. SURVIVED	NO. DIED	MORTALITY RATE (%)
Less than 1,000	1	11	91	3	16	84
1,001-1,500	29	20	40	28	8	22
1,501-2,000	86	6	6.5	77	5	6
2,001-2,500	68	3	4.2	64	3	4.4

SUMMARY AND CONCLUSIONS

1. Of forty-nine premature infants exposed to concentrations of oxygen from 60 to 64 per cent for thirty days and then abruptly removed from this environment, seventeen infants developed partial and eight infants complete retinal detachment (blindness).

2. Of thirty-four premature infants exposed to low concentrations of oxygen (30 per cent) for a similar period, only one infant developed partial retinal detachment which subsequently reattached and none developed complete retinal detachment.

3. When oxygen therapy was restricted to definite needs as outlined herein, retrolental fibroplasia, with the exception of one infant who showed early retinal vascular changes which subsequently s u b s i d e d, disappeared from the Premature Unit.

4. The restriction of oxygen therapy to definite needs exerted no deleterious effect on the mortality rate.

5. The evidence presented supports published data, indicating that the development of retrolental fibroplasia is, in some way, related to the prolonged use of high concentrations of oxygen.

Grateful appreciation is expressed to Dr. Meyer H. Riwchun, for his helpful advice in this project. We are also indebted to Mr. John Greene and his staff of the Greene-Kellogg Oxygen Service for helping with the oxygen analysis organization.

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ANDROGENIC PRECOCITY AND CONGENITAL CEREBRAL CORTICAL ATROPHY

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IN 1950 Perloff and Nodine[1] described four cases of congenital spastic quadriplegia associated with the premature development of pubic hair and elevated urinary 17-ketosteroid levels. There have been several previous reports in the literature[2-4] of precocious puberty associated with hypothalamic lesions; however, the cases reported in 1950 differed in that they manifested androgenic precocity or premature adrenarche rather than premature puberty. None of these patients had signs of an intracranial tumor and all four showed evidence of diffuse severe brain damage on electroencephalogram and x-ray. In addition, widely spaced eyes were noted in three of the four children which was striking enough to give them the appearance of being members of the same family. All of the children had pubic hair and one of them, a boy 8 years of age, had axillary hair. Two of the three females in the series, one 5 years and the other 3 years of age had hypertrophy of the clitoris. The other female, an infant of 15 months, had a normal-sized clitoris. The sole male in the series showed no penile enlargement.

Extensive laboratory studies were done on these children and three of the four had hormonal excretion studies performed. An elevation of the urinary 17-ketosteroid excretion was found in the three children on whom this test was done. Three specimens in the 8-year-old boy were reported as 5.0, 4.4, and 5.5 mg. per twenty-four hours. The 5-year-old girl had two 17-ketosteroid determinations, one reported as 1.8 mg. per twenty-four hours and the other as 4.0 mg. per twenty-four hours. The variation was probably due to inaccuracies in collections and illustrates the difficulty in obtaining a complete twenty-four-hour urine specimen in children. The 13-year-old girl had a urinary 17-ketosteroid excretion of 5.6 mg. per twenty-four hours, which was considered somewhat elevated for a female of this age. A laparotomy was done in two of the children and grossly no abnormalities were found. Adrenal biopsy in both cases was not deep enough to allow study of the zona reticularis; however, the zona glomerulosa and zona fasciculata showed abundant fat. An ovarian biopsy in one of the patients revealed cystic nests of granulosa cells. It was postulated at that time that damage to an adrenocortical center located in the midbrain was associated with the process which caused the brain damage. Since the function of this center was presumed to be inhibition of pituitary stimulation of the androgenic zone of the adrenal until about the time of puberty, its destruction would allow a premature adrenarche to occur. Since then, two additional examples of this syndrome have come to our attention.

From the Endocrine Clinics of the Philadelphia General Hospital.

CASE REPORTS

CASE 1.—R. G., a 6-year-old Negro female (Figs. 1 and 2) was admitted to the hospital because of anorexia and convulsions of one year's duration. She had never walked or talked and had apparently been blind since birth.

Fig. 1.

Fig. 2.

Examination revealed microcephalia and a marked hypertelorism was present. The eyes showed coarse bilateral nystagmoid movements with alternating divergence and searching movements, probably due to the poor visual acuity. The fundi revealed a widespread chorioretinitis. Spastic quadriplegia was present and bilateral Babinski and Hoffman signs were elicited. The clitoris, vagina, and uterus were of normal size. Moderate pubic and axillary hair was present. There was no other evidence of abnormal body hair. There was no breast development and the nipples were normal.

A complete blood count, sickling test, urinalysis, and serology were normal. The spinal fluid was clear and colorless with a white blood cell count of 19 per cubic millimeter, 88 per cent lymphocytes. Colloidal gold curve was 111210000. The spinal fluid sugar was 39 mg. per cent, chlorides 719 mg. per cent, and protein 19 mg. per cent. Toxoplasmosis and complement fixation tests were negative. A chest x-ray was negative and x-ray of both wrists revealed a bone age of about 4½ years. A skull x-ray revealed a small skull with normal outline of the pituitary fossa. There was evidence of an old fracture in the upper posterior right parietal region. Pneumocephalogram revealed a lack of visualization of the subarachnoid pathways. A diffuse abnormality was present on the electroencephalogram, with findings indicating organic cortical changes.

The twenty-four-hour urinary 17-ketosteroid level was 1.8 mg. per twenty-four hours (normal for this age, 0 to 1). Urinary estrogens were 13 mouse units, gonadotropins 0, and corticoids 53 micrograms, all normal levels for this age. A radioactive iodine uptake was 34 per cent and a serum protein-bound iodine 7 micrograms per cent.

CASE 2.—A. W., a 4-year-old Negro female, was admitted to the hospital because of convulsions and difficulty in swallowing of several years' duration. She had had several previous admissions for these symptoms.

Examination revealed a poorly nourished child with marked spasticity of all four limbs. It was impossible to be certain whether the child could see or hear. Hypertelorism was present. She was of normal height and weight for her age and there was a rather marked degree of muscular development. The floor-to-pubis length was one-half inch greater than the pubis-to-crown length. Pubic and axillary hair were present. The vagina, uterus, and clitoris were of normal size. There was no breast development present.

Routine laboratory studies were normal except for a hemoglobin of 9.1 gram per cent. A pneumoencephalogram revealed cerebrocortical atrophy. An electroencephalogram was diffusely abnormal with frequent high voltage slow waves, indicating diffuse organic cortical changes. A chest x-ray and an x-ray of the skull were negative. There was a bone age of about 3½ years on x-ray. A radioactive iodine uptake was 31 per cent and the serum protein-bound iodine was 5.0 micrograms per cent. The serum cholesterol was 222 mg. per cent, and a glucose tolerance test was normal.

The urinary 17-ketosteroid excretion was 2.0 mg. per twenty-four hours. The urinary estrogens were less than 13 MU, gonadotropins 0, and corticoids 125 micrograms.

DISCUSSION

These patients appear to be instances of the syndrome described by Perloff and Nodine in 1950, consisting of diffuse brain damage, spastic quadriplegia, hypertelorism, and androgenic precocity as evidenced by the premature growth of pubic and axillary hair and elevation of the 17-ketosteroid excretion.

True precocious puberty is associated with breast enlargement, menstruation, and possibly ovulation in the female and with spermatogenesis and testicular enlargement in the male. Neither the four cases described by Perloff and Nodine nor the two cases presented here fulfill the criteria of precocious puberty. However, they all showed evidence of premature androgenic activity.

The growth of pubic and axillary hair in the female appears to be primarily dependent on adrenal androgen production. There is no general agreement on this point, however, and there are some who feel the

gonadal steroids are responsible for this hair growth.[5] However, of the previous series and ours, five of the patients were female and none showed other signs of estrogenic activity. In addition, except for one female in the Perloff series who was 13 years of age and who had a twenty-four-hour estrogen level of 27 MU, none of the other children had estrogen levels greater than 13 MU. In the normal female there is no growth of axillary or pubic hair nor any significant excretion of 17-ketosteroids until about the time of puberty. The female with Addison's disease excretes practically no urinary 17-ketosteroids and has no growth of axillary and pubic hair.[6]

Prior to the age of 8 to 10 years the 17-ketosteroids excretion is usually below 1 mg. At about this time, which is often referred to as the adrenarche, the adrenal glands begin to produce increasing amounts of androgen, usually reaching adult levels by 18 years of age. The adrenal gland in childhood is capable of producing larger amounts of androgen than is normally produced since the 17-ketosteroid excretion will rise appreciably in children following stimulation with ACTH.[7] What brings about the increased production of 17-ketosteroids at the time of the adrenarche is still a matter of conjecture; however, it is possible that pituitary stimulation of adrenal androgenic activity is initiated at this time.

Silverman and associates[12] have described a series of thirty-seven normal prepubertal children with premature pubic hair. Many of these children had 17-ketosteroid levels that would be normal in adolescence. It was felt that this was just a benign constitutional variation in the pattern of normal adolescent development. In this series seven of the patients were mentally deficient but there was no mention of the occurrence of brain damage. It was thought that the mental defect had no etiological role in the appearance of the premature pubarche (adrenarche). Wilkins[11] states that "premature pubarche is a variation in the pattern of sexual development which may be due to either increased sensitivity of the hair follicles to androgenic stimulation or early elaboration of adrenal androgens."

It has been suggested that precocious puberty associated with hypothalamic tumors may be brought about by the destruction of neural pathways which normally serve to inhibit the nerve impulses passing to the pituitary.[8] With the removal of neural inhibition, due to destruction of inhibitory pathways by the tumor, increased gonadotropin production brings about the development of a premature puberty. Similar theoretical reasoning has been applied in attempting to explain the appearance of a premature adrenarche in children with diffuse brain damage.[1] Assuming the destruction of centers which inhibit pituitary stimulation of adrenal androgenic activity until the time of puberty, androgenic stimulation would, in the prepubertal child, cause the premature appearance of changes commonly associated with adrenal androgen production.

There appears to be a difference between these cases and the adrenal hyperplasia of childhood, either congenital or acquired. The most generally accepted explanation for the pathogenesis of congenital adrenal hyperplasia is that there is an enzymatic defect in the formation of com-

pound F in the adrenal gland. Since compound F is the most important of the adrenal hormones in the inhibition of pituitary production of ACTH, a deficiency of this hormone allows increased ACTH secretion which in turn brings about increased production of adrenal androgen.[9, 10] If the onset is prenatal, before the fifth fetal month, female pseudohermaphrodism will result. Since the urogenital sinus becomes differentiated by this time, the onset of adrenal hyperplasia after the fifth fetal month usually leads only to virilization.[11] These children also show increased epiphyseal growth, hypertrophy of the clitoris, and a deepening of the voice. Facial and body hirsutism along with acne are often common accompanying signs of excessive adrenal androgenicity.

In the previous series and the cases reported by us there was no increase in bone age and no other signs of excessive androgenic activity. Rather, there seems to be an early appearance of changes that would be normal at the time of puberty. The possibility that these children exhibit mild forms of adrenal hyperplasia exists but is unlikely. If factors responsible for the brain damage also produced a degree of adrenal damage, then adrenal hyperplasia might result from a lack of inhibition of ACTH production by the adrenal cortex. In view of the mild degree of androgenicity in these children, it does not appear that adrenal hyperplasia has occurred, but rather what would be a normal level of adrenal androgenic activity at puberty has taken place too early.

Only the passage of time and the reporting of further cases will establish this as a syndrome, but the theoretical explanation offered would seem to be a reasonable one.

SUMMARY

Two patients are reported with diffuse severe brain damage associated with the premature development of pubic hair. Four similar cases have been previously reported. Destruction of centers which normally serve to inhibit pituitary stimulation of adrenal androgenic activity, allowing a premature adrenarche to occur, is offered as a possible explanation.

We are grateful to the chiefs of the Department of Pediatrics at the Philadelphia General Hospital on whose wards these patients were seen.

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SARCOMA OF THE PROSTATE

In a Fourteen-Month-Old Child

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MALIGNANT tumors in children are not frequently seen. Sarcoma of the prostate is among the rarest tumors found in children or in adults. In 1954 seventy-three cases of malignant tumors in children were reported from the John E. Jennings Hospital, covering a period of twenty-two years. Only one of them was sarcoma of the prostate.[1] Among 31,882 deaths from prostatic malignancy in the United States studied by Stirling and Ash,[2] only thirty-five were sarcoma, a ratio of approximately 1:1,000. Very little has been written on this subject in modern textbooks. Two hundred twenty-five cases of sarcoma of the prostate have been reported in the literature up to the present writing. The youngest patient was 4 months old, the oldest 88 years. The majority of cases occurred in the first decade of life.

CASE REPORT

On Aug. 30, 1948, a 14-month-old white male infant was admitted to the John E. Jennings Hospital with a diagnosis of sarcoma of the prostate. Three weeks previous to admission the parents noted that the patient experienced pain on urination and to a lesser extent on defecation. He would double up and clutch his perineum. A doctor was called in who admitted the patient to Prospect Heights Hospital on Aug. 24, 1948. Rectal examination revealed a mass in the region of the prostate, encroaching on the anterior rectal wall. A small rubber catheter was introduced into the urethra for two inches but was blocked by an obstruction. A small filiform bougie met the same obstruction, but was able to pass into the bladder and 15 c.c. of straw-colored urine was obtained for examination. The specific gravity was 1.0, acetone 3 plus, with occasional white and red blood cells, epithelial cells, and few bacteria. X-ray examination of opaque cystogram on August 26 revealed the bladder to be moderately filled. The base of the bladder appeared elevated by a mass in the prostatic area. Subcutaneous urography was reported as "normally functioning urinary tract; no evidence of pathology in the upper urinary tract; suggestive evidence of a mass extrinsic in the base of the bladder, possibly in the prostatic area." The following day a "perineal exploration" was performed and a biopsy taken from the prostatic mass. The histologic report by Dr. Silik H. Polayes, pathologist, was "spindle-cell sarcoma" (Fig. 1). The patient was then transferred to the John E. Jennings Hospital on Aug. 30, 1948, in poor condition, with a final diagnosis of spindle-cell sarcoma of the prostate.

Physical examination of the patient and the histological studies of the slides by Dr. Herman Bolker, pathologist, confirmed the clinical and pathological diagnosis. The infant was poorly nourished, dehydrated, the abdomen was moderately distended, the thighs were tightly flexed against

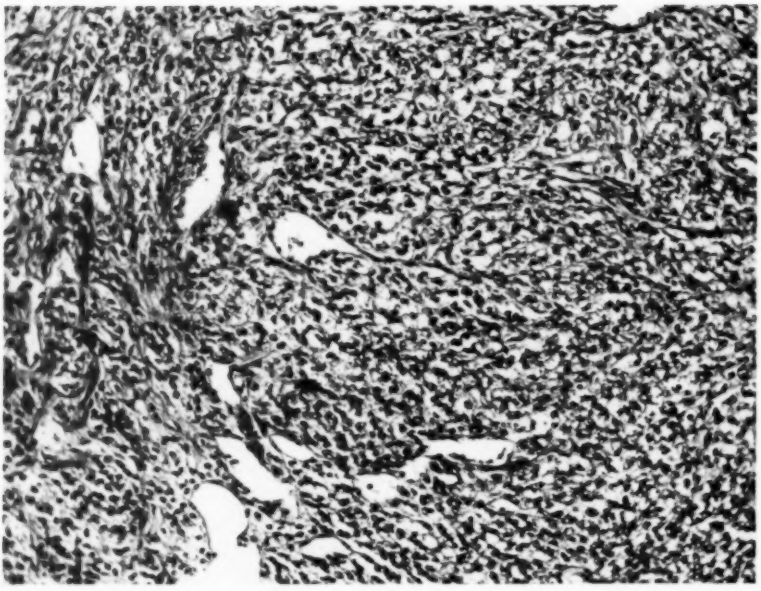

Fig. 1.—Photomicrograph showing sheets of polyhedral and spindle-shaped tumor cells in a vascular stroma. (×220; reduced ⅙.)

Fig. 2.—Perineal area where the prostate was explored, showing large fungating growth protruding from the former incision.

the abdomen, and the perineal wound was still draining degenerated material. Rectal examination revealed a large boggy mass in the region of the prostate, partially occluding the rectal lumen by pressing on the anterior rectal wall and extending upward to the promontory of the sacrum. Proctoscopic examination revealed no intrinsic pathology. The blood count showed a relatively secondary anemia and a moderate leukocytosis. The blood chemistry was within normal limits. The temperature varied from 98° to 101° F., the pulse from 70 to 130.

The infant received intravenous 5 per cent glucose solution, vitamin, penicillin, and Prostigmin. He was kept on a liquid diet, given a blood transfusion, and was made comfortable with phenobarbital and Demerol. On September 2 the perineal wound was enlarged and twelve 35 mm. needles, each containing 2 mg. of radium elements, were inserted into the prostatic mass, followed two weeks later by deep x-ray therapy. However, his condition became progressively worse. The pelvic mass became larger until it reached the umbilicus. The abdomen was distended with a marked dilatation of the superficial veins, caput medusae. Below, the tumor completely compressed the rectal opening and protruded through the perineal wound in the form of a large fungating growth, completely obliterating the anal opening (Fig. 2). On Nov. 8, 1948, a left colostomy was performed. The colostomy functioned well, but the condition of the infant became worse. He developed a marked dyspnea and died on Dec. 19, 1948, four months after onset of symptoms. Consent for autopsy could not be obtained.

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On St. Vitus's Dance

This is a kind of convulsion, which attacks boys and girls from the tenth year to the time of puberty. It first shows itself by limping or unsteadiness in one of the legs, which the patient *drags*. The hand cannot be steady for a moment. It passes from one position to another by a convulsive movement, however much the patient may strive to the contrary. Before he can raise a cup to his lips, he makes as many gesticulations as a mountebank; since he does not move it in a straight line, but has his hand drawn aside by spasms, until by some good fortune he brings it at last to his mouth. He then gulps it off at once, so suddenly and so greedily as to look as if he were trying to amuse the lookers-on.

From THOMAS SYDENHAM (1624-1689).

PHTHIRIASIS PALPEBRARUM (PHTHIARIS CILIARIS)

HENRY HARRIS PERLMAN, M.D., SYLVIO FRAGA, M.D., AND MARCO MEDINA, M.D.
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AN ODD dermatological condition occasionally encountered in children is an infestation of the eyelashes with the *Pediculus pubis*, or crab lice, and its ova.

CASE REPORT

The patient, a white girl, aged 6 years, was first seen at the dermatological-pediatric outpatient department on Oct. 17, 1955. The condition had first been noticed by the mother five months previously. The past history was irrelevant. Upon examination numerous grayish-white bodies about the size of millet seeds were found on the eyelashes of both lids. Most of the bodies were located approximately close to the margin of the lid, although some were seen to be situated distally on the eyelashes. Several of the nits could be dislodged from the eyelashes by means of a fine pair of tweezers. At the time of the examination the mother stated that she was able to see several lice on the hair of the scalp. However, at the time of the initial examination at our clinic and on subsequent examinations, no evidence of infestation of the scalp hairs could be found.

There was no itching or other sign of discomfort, although a mild marginal blepharitis was present. Both conjunctivae (of the right and left lower lids) were slightly injected. Several oval-shaped bodies were removed and examined under a microscope. These conformed to the pubic louse, and specimens sent to the United States Department of Agriculture, Research Branch of Entomology, were confirmed as the crab or pubic louse, *Phthirus pubis* (L.). Under the treatment outlined, the condition was entirely cured, the blepharitis and conjunctivitis disappearing two weeks and four days after the treatment described. Search was made for the possibility of pediculosis pubis in other members of the family with negative result. Both parents told that the child had been in the habit of spending week ends with grandparents.

From the Dermatological-Pediatric Department of The Skin and Cancer Hospital.

DISCUSSION

Logically, one would think that the *Pediculus capitis* would be the offending parasite, since the pubic area is remote from the eyelashes. The *P. pubis* is not invariably the offending parasite on the eyelashes. Hill,[1] in a child aged 2 years, found male and female specimens of the *P. capitis*. In Hill's opinion, this type of parasite was purely accidental on the eyelashes, their presence there attributable to scalp hair in a "spring cleaning" from which one or two ova had fallen on the lashes to become a colony. Goldman and Friedman[2] reported a case of a 19-month-old infant in whom numerous grayish and light brown specks were embedded in the scalp and firmly attached to the hairs above the ears, over the posteervical area and over a small area just inside the hairline. The eyebrows were entirely clear, but the eyelashes were beaded with little whitish bumps and dark brown spots along the

margins of the lids. Slight marginal blepharitis was present. In this case the spots on the scalp proved to be the pubic louse *(P. pubis)*.

A survey of literature discloses that infestation of the eyelashes with the pediculus, while not common, is by no means rare.

In 1934, Friedman and Wright[3] reported the case of a 19-year-old male college student who complained of blepharitis affecting only the right eye. Closer inspection of the margin of the eyelid and the eyelashes aroused a suspicion that the peculiar dotlike bodies observed thereon were ova. As many as four ova were found attached to some lashes of the upper lid. No pediculi were found. Microscopic examinations of the parasite disclosed it to be *P. pubis*.

Goldman and Friedman[2] state: "In spite of the fact that the pubic louse *(Phthirus pubis)* may be found on the eyebrows and on the eyelashes of patients with extensive infection, involvement of the scalp is extremely rare." These investigators state further that only ten cases have been reported in the foreign literature. Boase[4] reported four cases of phthiriasis palpebrarum, the youngest case in a youth, aged 17 years, and the oldest in a woman, aged about 40 years; the other two were males in their early twenties. Heilesen and Lindgren[5] collected seven cases of infection with *P. pubis* with rare localization in the

Fig. 1.—Phthiriasis palpebrarum. Ovum attached to the eyelash by a chitinous substance. (×20.)

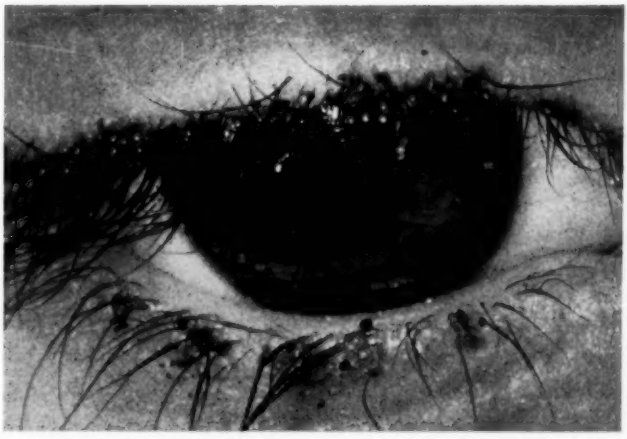

Fig. 2.—Phthiriasis palpebrarum in a 6-year-old white girl. Numerous ova attached to the proximal ends of the eyelashes of the upper and lower lids.

cilia, supercilia, and capillitum. Viallenfont[6] reported a case of ciliary pediculosis in a 4-year-old child who was entirely asymptomatic. Angnello[7] reported four cases of parasitic blepharitis due to the *P. pubis*.

In children the most common cause for pediculosis of the eyelashes is the pubic louse. The condition is generally acquired through contact, especially while sleeping with infested individuals. In Goldman and Friedman's[2] case, a nursemaid was suspected as the source of the infestation. Ronchese[8] states that "a male or female breast and the axillae are the most common source of infantile pediculosis of the eyelids." He reported pediculosis of the eyelashes due to infestation with *P. pubis* in a 1½-year-old girl. He adds that recurrences are due exclusively to reinfestation from the same source (parents, nurse, or attendant).

Fortunately the ova attached to the eyelashes are not firmly adherent as they are on the scalp, and for this reason they may be removed the more easily. In this respect the advice offered by Ronchese[8] is timely and simple. He states: "The infant's head is held as firmly as possible with the help of assistants. In spite of batting eyelids, screams and tears, the struggle will be a brief one and will end to everybody's satisfaction. The lice are easily picked out with a pair of cilia forceps (tweezers) or trachoma forceps (not just any forceps). They are slipped out, and the ova (nits) as well. The removal of the nits is facilitated by the infant's tears. If an eyelash comes out with the nit, no harm is done, for another will grow in the same place in due time."

SUMMARY

A case of phthiriasis palpebrarum in a 6-year-old white school child is reported. The responsible parasite proved to be the crab or pubic louse, *Phthirus pubis*. A cure resulted in about two and one-half weeks by using wet compresses of a 4 per cent solution of boric acid applied directly to the eyelids and eyelashes, which were followed by inunction with a 1 per cent yellow oxide of mercury ointment applied three times daily. Many of the ova were removed with a fine tweezers. The literature is reviewed, and the diagnosis and management have been discussed.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

AN Anglo-Saxon boy, aged 5 years 1 month, was admitted to the hospital because of jaundice since 3 months of age.

The mother received several blood transfusions during the pregnancy because of a chronic anemia. There were no reactions to these transfusions. The child was described as normal at birth and was well until 3 months of age, when progressive jaundice and intermittent pale-colored stools were noted. He was seen at another hospital at the age of 9 months. He was jaundiced. His liver was 4 fingerbreadths down and the spleen was not palpable. His urine was negative except for a 2 plus reaction for bile. It contained no urobilinogen. Routine examination of the peripheral blood was normal. Total serum bilirubin was 5.3 mg. with a direct of 3.2. Laparotomy was performed at that time but the child continued to have intermittent jaundice until the time of admission here, although he was never really free of jaundice. He had marked itching of the skin. The urine was dark brown or yellow. He complained of abdominal pain frequently but the nature of this complaint was not satisfactorily described. His appetite, however, was good. He was given vitamin K because of a bleeding tendency.

He had immunizations at 3 months of age, and the mother related this to the onset of jaundice. He had "asthmatic" attacks until about 3 years of age. He was not susceptible to infection. He was somewhat retarded in his development, walking at 22 months and beginning to talk at 2 years.

The mother was 39 years old. She has had anemia and a mild jaundice all her life. A maternal uncle had anemia which was not helped by splenectomy. A maternal grandfather had gall bladder trouble and was jaundiced during the last two or three years of his life. A maternal grandmother and two maternal aunts are well. The child has a 13-year-old sister who is well.

On admission the temperature was 98.4° F., pulse 88, respiration 22, and the blood pressure was 96/48. The boy was irritable, somewhat small, but well nourished. The skin showed marked icterus as well as brownish pigmentation scattered throughout. There was a mild dermatitis secondary to scratching the skin. The head was not remarkable. The sclerae were icteric. The tonsils were somewhat hypertrophied and chronically inflamed. There was no glandular enlargement. The chest was clear to percussion and auscultation. The

heart was normal. The abdomen was distended and tympanitic but not tender. The liver edge was hard and irregular, and was palpated 3 to 4 cm. below the right costal margin. The spleen was not satisfactorily palpated but was thought to be enlarged. The extremities showed no clubbing or edema.

The urine was yellow and cloudy with a pH of 5.5. The specific gravity was 1.017, albumin 0, sugar 0, bile 4 plus, urobilinogen positive 1:16. Examination of the blood disclosed a hemoglobin of 13 grams, red blood cells 4.2 million, white blood cells 8,400; 37 polymorphonuclear cells, 3 band forms, 1 eosinophil, 43 lymphocytes, 5 monocytes, 11 atypical lymphocytes. The red blood cells appeared normal, platelet count 303,000. The total serum bilirubin was 5.4 mg. per cent, with 3.3 mg. per cent direct. Thymol turbidity reaction was 0, thymol flocculation 0, cephalin flocculation 0, prothrombin time 13 sec., control 13 sec. Bone marrow: total nucleated cells 500, megakaryocytes adequate. Myelocytes: neutrophilic myelocytes 1, eosinophilic myelocytes 8, neutrophilic metamyelocytes 1, eosinophilic metamyelocytes 4; neutrophilic band forms 15; neutrophilic polymorphonuclears 20, lymphocytes 20, monocytes 3; proerythroblasts 2; erythroblasts 10; normoblasts 20; erythrocytes: myelocytes 1:2. Spherocytes were present in the smear. The fragility tests were as follows:

Fragilities	*Osmotic*	*Mechanical*
Mother		
Nonincubated	50% hemolysis at 0.40	
24 hr. incubated	50% hemolysis at 0.41	5.5%
48 hr. incubated	50% hemolysis at 0.44	34.0%
	Beginning at 0.80, complete at 0.18	
Patient		
(10 days after transfusion)	50% hemolysis at 0.40	3.1%
Nonincubated	50% hemolysis at 0.50	28.0%
24 hr. incubated	Beginning at 0.80, complete at 0.10	

Two operations were performed on this child.

DISCUSSION

DR. SIDNEY FARBER.—The discussion will be initiated by Dr. Sydney Gellis.

DR. SYDNEY GELLIS.—This was an Anglo-Saxon boy, aged 5 years 1 month, who had had jaundice since the age of 3 months. We will stop there. Anglo-Saxon suggests, but does not prove, that his jaundice might have not been due to Cooley's anemia or sickle-cell anemia. His mother received several blood transfusions during pregnancy because of a chronic anemia. Can we relate either of these facts to the offspring's jaundice beginning at 3 months? In the first place we mention of course the virus of homologous serum hepatitis, which might well have been introduced to the mother with these transfusions. The interval of three months from birth for the jaundice to appear is still in keeping with homologous serum hepatitis transmitted through the placenta, since the incubation period may be as long as six months. We do not know actually the timing of the transfusions that she received, so that this is a possibility. We have discussed at previous meetings here the syndrome of neonatal hepatitis, which appears to be due to the transmission of the virus of homologous serum hepatitis from a carrier mother to the fetus. It would be very interesting to know the mother's liver function tests. Probably they were

not done. In none of our fifty cases of neonatal hepatitis have we had an onset of disease as late as this patient. However, this still could explain the obstructive type of jaundice. We will elaborate on that later. We are told nothing as to the nature of her anemia, but we must consider that this boy's jaundice may basically be due to an anemia that is hereditary. The child was described as normal at birth and was well until 3 months of age. The long interval when he appeared well, as I say, argues against homologous serum hepatitis though it does not rule it out. Age 3 months seems to be too early for an infectious hepatitis to have developed. I have never seen these in family outbreaks in such a young infant. The absence of early jaundice and anemia eliminates erythroblastosis, which should give jaundice shortly after birth. We always have to think of galactosemia as an explanation for an obstructive jaundice in the young infant; but it always seems to start right after one expects physiologic jaundice to disappear. I would think that one could completely eliminate that diagnosis. Jaundice due to inherited anemia cannot be eliminated. It is rare for congenital hemolytic anemias, sickle-cell anemia, for example, to give rise to jaundice in the early days of life. It typically gives rise to jaundice after the newborn period is over.

The protocol states that intermittent pale-colored stools and progressive jaundice were present. These two statements do not hang together too well; the stools either had to be continually pale and his jaundice progressive or they were intermittently pale and his jaundice had to vary. In patients with atresia of the bile duct one often gets a history of intermittent pale stools. However, the history cannot be trusted, for testing of the darker stools for bile still gives a negative test. Also, the mother's history about progression or variation of jaundice is never a reliable one. We see many infants with atresia of the bile ducts where the mother swears that the jaundice has become much lighter or darker; I doubt very much if such stories are true. On the basis of the history of light stools and jaundice we have to turn to an obstructive process to explain the jaundice. The commonest cause would be atresia of the bile ducts, but if we can accept the story that he was well for three months and not icteric, I think we could try to eliminate atresia as a diagnosis, for I cannot see how a patient could be nonicteric for such a long time with atresia of the bile ducts. He could, however, have a partial or intermittent obstruction, in which case some of the stools should have been dark and the jaundice should not have been progressive. Tumors or cysts could give such a picture, especially a choledochal cyst, and we will have to come back to that possibility.

Can his obstructive jaundice fit in with anemia which is so important in this story? In hemolytic anemias one of the important causes for an obstructive type of jaundice is of course the development of stones, and this is the chief basis for finding stones in the pediatric age group. This child seems too young to have developed this complication, and we are not impressed as we go on in the story with severity of anemia, but the diagnosis cannot be eliminated at this stage of the story. Finally, hepatitis may cause an intermittent type of obstruction, so that at this point the only diagnosis I again

feel I can completely eliminate from the differential is atresia of the bile ducts.

The boy was seen at another hospital at the age of 9 months. I suspect the test for urobilinogen was based on a single specimen, which is not very satisfactory; but it does suggest that total obstruction was present. However, his serum bilirubin was only 5.3 mg. per cent with 3.2 of this direct. If he were totally obstructed from the age of 3 months his serum bilirubin by 9 months should have been much higher. If he has a hemolytic anemia he has to have an obstructive process also; otherwise he should have no bile in his urine and his stools should be normal in color. The lack of enlargement of the spleen at this time would be slightly against an underlying anemia. The large size of his liver, however, suggests intrahepatic disease, as with hepatitis, tumor, cirrhosis, or an intermittent extrahepatic obstructive process. Extrahepatic bile ducts, choledochal cysts, or a tumor pressing against the extrahepatic ducts would have been discovered. We can eliminate these three diagnoses. Intrahepatic tumors may be eliminated because I suspect that if a child had a primary tumor in the liver he would not have survived for over five years. I think I am left with the diagnosis of hepatitis, cirrhosis, or anemia, with intrahepatic obstruction. Whatever was accomplished at the first laparotomy failed to be of significance therapeutically, for he continued to have fluctuating jaundice until the time of admission to this hospital. He had marked itching of the skin, which indicates biliary obstruction. Moreover, the urine was dark brown or yellow, suggesting that intermittent obstruction was present. He complained of abdominal pain, which could come from liver disease, gallstones, tumor, or splenic infarcts, with hemolytic disease. A good appetite is not found in patients with severe intrahepatic disease, and favors hemolysis as his primary difficulty. He was given vitamin K because of a bleeding tendency. He might not have absorbed vitamin K because he had an obstruction, or he could not utilize it because the liver was badly damaged.

I cannot correlate the "asthmatic" attacks with his basic disease; actually, jaundice is supposed to benefit uncomplicated asthma. The histories of the mother and maternal uncle are suggestive of some type of anemia such as sickle-cell, Cooley's, or nonspherocytic hemolytic anemia, rather than congenital hemolytic anemia which might be helped by splenectomy. The maternal grandfather had gall bladder trouble and was jaundiced during the last two or three years of his life, giving us an extremely strong family history. His well-nourished state argues against hepatitis, cirrhosis, or tumor, for if these diseases were primary and existed since the age of 3 months he should be very poorly nourished. If the skin pigmentation was patchy and we are dealing with an inherited anemia, it suggests to me the possibility of Fanconi's syndrome, which is a congenital anemia, aplastic in type, and is accompanied by brownish spots. The diagnosis is unlikely in this boy, since these patients usually have multiple congenital anomalies such as microcephaly, strabismus, abnormalities of fingers and toes, or any suggestion of an aplastic type of anemia. The description of the liver strongly suggests that fibrosis is present.

The laboratory data reveal nothing striking in the way of an anemia, which is disappointing in view of the family history. The liver function tests performed were normal except for his serum bilirubins which suggested a straight basic type of obstruction. There was a striking increase in mechanical fragilities following incubation in the mother and in the child. I am also struck by the fact that the only fragility tests on the patient were done 10 days after transfusion. I will want to know Dr. Diamond's interpretation of the fragility tests.

DR. LOUIS K. DIAMOND.—There was one fragility test done after operation. The fragilities on the mother, as we interpret them, were essentially normal, but the mechanical fragility was somewhat increased after incubation. The patient's fragility tests also were essentially normal. The reticulocyte count on the patient was consistent with very low hematopoietic response; the bone marrow showed an increased erythroid to myeloid ratio; instead of 1:4, it was about 1:2. So our interpretation would be that this boy did not have the typical increased fragility of hereditary spherocytosis; neither did his mother.

DR. GELLIS.—Are there any x-rays?

DR. E. B. D. NEUHAUSER.—There is only one film, which I will show if you promise not to be prejudiced by it.

We never saw this patient until operation had been carried out, Dr. Gellis, but we took a film after the introduction of an opaque medium into the gall bladder through a catheter. It just happens to be a magnificent study that confirms your impression that there is nothing here suggesting mechanical obstruction of any of the major ducts.

DR. GELLIS.—I will have to guess at these operations. First, I would guess that they did an exploratory laparotomy. I would guess that the surgical service felt that this child had an obstructive type of jaundice. They found no evidence of obstruction and then took a piece of liver for biopsy. I suspect that the second operation was a splenectomy though I cannot be sure that perhaps a shunt was done.

In summary, we have here a patient with a family history of jaundice and anemia in an uncle unrelieved by splenectomy; and jaundice and anemia in his mother. We are not told that the mother ever had a splenectomy. It would help to know. Our patient had jaundice beginning at 3 months, obstructive in nature. He obviously had to have something wrong besides an inherited anemia. Obviously, if he had an inherited type of anemia—Cooley's, sickle-cell, or elliptical cell anemia, none of which is likely on the basis of the information—my diagnosis is narrowed down to a congenital spherocytic anemia or a hereditary nonspherocytic anemia. The latter seems more likely, since splenectomy did not help the uncle, and notoriously in hereditary nonspherocytic anemia a splenectomy is of no help. I am impressed with the fact that both in the mother and in the child mechanical fragilities increased quite markedly following incubation, which is a strong argument for a diagnosis of congenital spherocytic anemia, in that most of the patients with nonspherocytic anemia do not have such a striking increase in mechanical fragility following incubation. As to the obstructive jaundice, this could be caused by stones, but we have no evidence of them because if

he had stones they should have been found and they would not have done a second operation. It could be caused by intrahepatic stasis with inspissation of bile and formation of bile thrombi. I would vote against that because there was no severe anemia at any time. Finally, I would say, on the information given, the boy had congenital spherocytic anemia. I think he has a diffuse intrahepatic disease consisting of either a diffuse hepatitis or a cholangiolitis. I would favor a diffuse hepatitis as my first bet. Regarding the operations, I think a biopsy of the liver was taken and a splenectomy was done.

A PHYSICIAN.—Would splenectomy aid a hereditary nonspherocytic anemia?

DR. GELLIS.—No. I think that if he had a hereditary nonspherocytic anemia they made a mistake in removing his spleen. I suspect they made no mistake, and that he had congenital spherocytic anemia that should be helped by splenectomy. But if that is true, why did the mother not have her spleen removed? Or if her spleen was removed why was she not better?

DR. DIAMOND.—One point might help you. Concerning the fragility tests, we feel that the osmotic fragility in our hands is a more accurate test than the mechanical fragility and that we have found increased mechanical fragility more frequently without any suitable explanation. We have practically never found any real increase in osmotic fragility without reasons. The osmotic fragilities here were definitely within normal range. The spherocytes present in the smear were seen after transfusion. There was no marked increase in the number of spherocytes. We discounted this as having no diagnostic import in this child's case.

DR. GELLIS.—May I ask if you did a smear on the mother, and did she have spherocytes?

DR. DIAMOND.—Yes, we did, and she had no spherocytes.

DR. GELLIS.—Then, without any trouble, I change my diagnosis to hereditary nonspherocytic anemia.

DR. DIAMOND.—Of course, she never had splenectomy; but it was well established that her brother, who had had splenectomy four or five years previously, had not benefited from the operation.

DR. GELLIS.—On that basis, Dr. Farber, my final diagnosis is hereditary nonspherocytic anemia in uncle, mother, and boy, diffuse intrahepatic disease consisting of a not too severe hepatitis. The operations were liver biopsy and splenectomy.

DR. FARBER.—May I ask before you retire, why do you introduce hepatitis?

DR. GELLIS.—I have to explain the obstructive type of jaundice, and the large, firm liver. No one has given me any history of real severe attacks of anemia in this boy, which would give rise perhaps to a fatty liver, give rise to fibrosis, so I am falling back on some other explanation for these findings.

DR. FARBER.—So you are really thinking of two separate conditions, unrelated.

DR. GELLIS.—I would think I have to.

DR. JOHN CRAIG.—Would you believe, Dr. Gellis, that a patient could go this long with familial jaundice and hepatitis without getting into more

obvious obstructive cirrhotic symptoms?

DR. GELLIS.—We have had a boy here recently with just that.

DR. CHARLES JANEWAY.—I would like to ask one question about the fragility. I think the shape of the curve is of some importance as well as the point of 50 per cent hemolysis. In other words, I wonder whether there was a small percentage of the population of cells that showed a marked increase in fragility?

DR. DIAMOND.—There probably was.

DR. JANEWAY.—On the basis of a marked shift of part of the population?

DR. DIAMOND.—That is found frequently in patients with some splenomegaly. It may be completely nonspecific. You can get widened splenic sinusoidal spaces and increased destruction of a small portion of the total cell population. When seen by Dr. Robert Hartman about ten days after discharge from this hospital the boy had gained about 4½ pounds. The hemoglobin and the rest of the blood findings were the same as they were when discharged here. The jaundice appeared to have been less. The bilirubin was still around 3 mg. per cent six weeks after operation. It is said that splenectomy is not supposed to help persons with nonspherocytic hemolytic anemia. In this child it helped him somewhat.

DR. FARBER.—We are delighted that Sir Lionel Whitby is with us today. Would you like to speak on any part of this discussion?

SIR LIONEL WHITBY.—I speak with all diffidence, but what puzzled me about the case is that we saw some type of anemia, yet this patient does not appear to me to be anemic. And if this is a hemolytic anemia, the hemolysis is fairly active as judged by the degree of bilirubinemia. Nevertheless the reticulocytes were only 2.2 per cent. It might be that this ought really to be a case of diffuse hepatitis.

DR. CRAIG.—I would like to ask a leading question of Dr. Gellis. Why did you exclude familial hyperbilirubinemia?

DR. GELLIS.—That is easily excluded. In the first place, familial hyperbilirubinemia would have an increase only in the direct bilirubin and not in the indirect. There have been cases of familial nonspherocytic familial anemia that have been confused with hyperbilirubinemia. This boy's elevated direct bilirubin level eliminates that.

DR. DIAMOND.—I would like to tell you of some of the discussion we had after the first operation and before the second one. In the first place, regarding this diagnosis, this patient had been worked up very well previously by Dr. Hartman, who came to the conclusion that this was one of the group of so-called familial congenital nonspherocytic hemolytic jaundice. However, he was dissatisfied, as were we when the patient was here, by the fact that the patient continued to have jaundice and since the operation that had been done on the child when he was only 9 months old had not included a liver biopsy. In going over the child after the first operation here, and before the second, it seemed to us that we could not exclude at least some small element of increased hemolysis from the fact that there was an increase in the number of fragile cells judging by the curve. Dr. Robert Gross's working hypothesis was

Fig. 1.

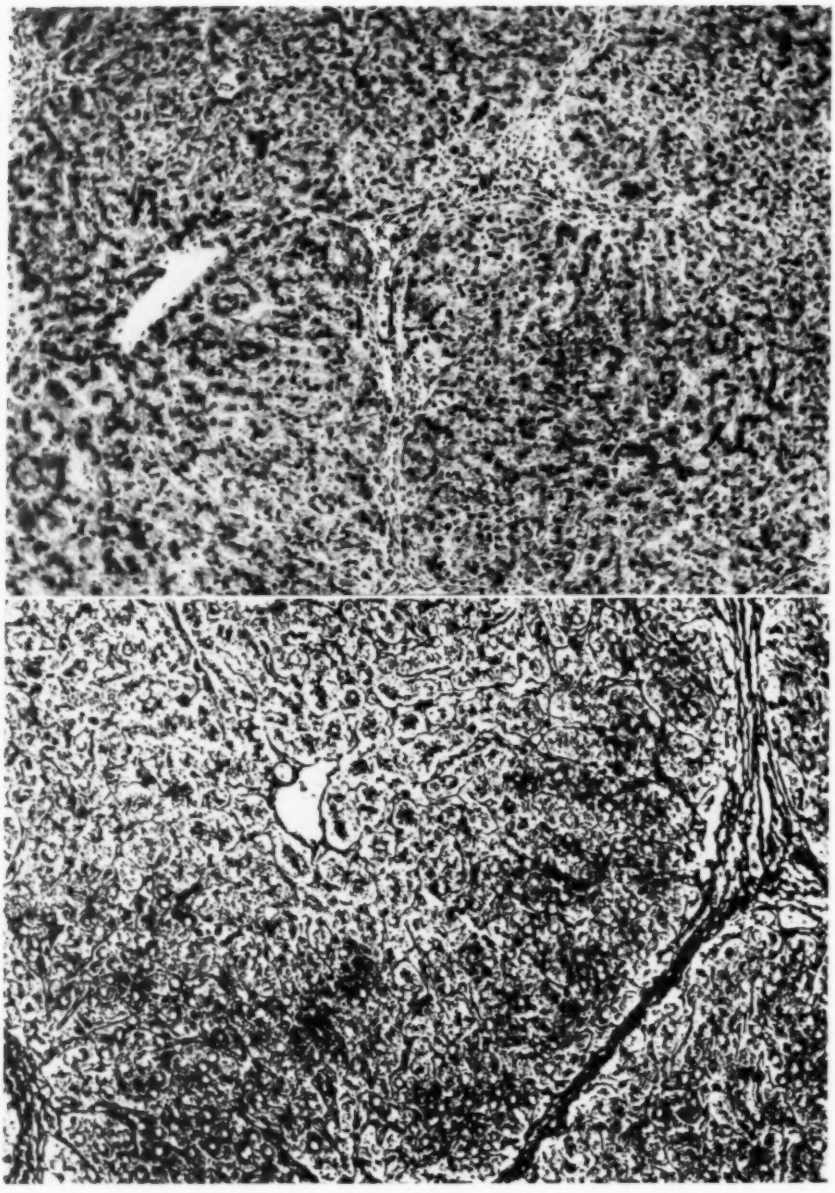

Fig. 2.

Fig. 1.—Liver. The slight distortion of the lobular pattern, minimal fibrosis, and intense hepatocellular segment deposition are seen. (Hematoxylin and eosin; ×110.)

Fig. 2.—Liver. There are fibrosis and silver deposition on the pigmentary granules in the center of the liver lobule. (Wilder's reticulum; ×200.)

that with evidence of liver disease and with increased hemolysis the patient might be benefited by splenectomy. This was discussed with the parents in the light of the uncle's failure to improve and the experience of Motulsky and associates[1] in hereditary nonspherocytic hemolytic disease. They point out that some of these patients are benefited by splenectomy though not as much as the patients with congenital spherocytic hemolytic disease.

increase in size or prominence. The liver biopsy was slightly nodular on gross examination, and the lobular pattern was not only accentuated, but distorted (Fig. 1). We believe that this pattern of fibrosis with distortion of the lobules is evidence of a mild degree of postnecrotic scarring. It cannot be said to represent cirrhosis. There was little evidence of any active inflammatory process in the liver. There was a minimal degree of bile stasis, thrombi being present only in

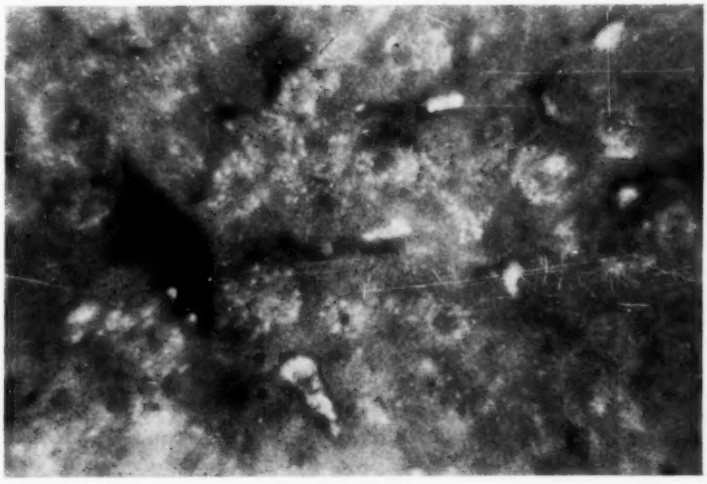

Fig. 3.—Liver. Autofluorescence in ultraviolet light is found in the pigment granules, in the parenchymal cells, and in the nongranulated Kupffer cells. Unstained. Photographed in ultraviolet light. (×400, approx.)

DR. FARBER.—Dr. Craig, will you describe the pathologic findings?

DR. CRAIG.—The spleen was only slightly over its normal weight and had the changes which have been described in hypersplenism.[2] This consists of the presence of a prominent marginal zone of the malpighian follicles, made up of immature lymphocytic forms. Only a small amount of hemosiderin was encountered with the reticuloendothelial cells of the sinusoids, and the cells showed only slight

the bile canaliculae. There was no evidence of the usual alterations seen in obstructive jaundice. The parenchymal cells were remarkable because of the presence of a large amount of pigment, which was not hemosiderin, but which had a number of unusual properties. It took a positive silver stain (Fig. 2), but did not take the usual stains for bile. It was not acid-fast and therefore cannot be considered to be ceroid. It did not stain with a simple fat stain, although there

TABLE I. COMPARISONS OF CLINICAL FEATURES OF THIS CASE, THE "CHRONIC IDIOPATHIC JAUNDICE" OF DUBIN AND JOHNSON, AND FAMILIAL HYPERBILIRUBINEMIA

	DUBIN AND JOHNSON	THIS CASE	FAMILIAL HYPERBILIRUBINEMIA
Chronic intermittent jaundice	+	+	+
Abdominal pain	+	+	0
Enlarged liver	+	+	0
Elevated direct bilirubin	+	+	+
Elevated indirect	+	+	0
Urine bile	+	+	0
Urobilinogen	+	+	0
Positive flocculation tests	+	0	0
Anemia	+	+	0
Spherocytosis	–	±	0

TABLE II. COMPARISON OF LIVER HISTOLOGY OF THIS CASE AND "CHRONIC IDIOPATHIC JAUNDICE" OF DUBIN AND JOHNSON

	DUBIN AND JOHNSON	THIS CASE
Unidentified liver cell pigment	+	+
Autofluorescence	+	+
Iron pigment	–	–
Acid-fast pigment	±	–
Periodate leukofuchsin	±	–
Resistance to solvents	+	+
Bleached by hydrogen peroxide	+	+
Bile canalicular stasis	–	+
Mild liver fibrosis	+	+

were small amounts of fat within the Kupffer cells. It gave a reddish-brown fluorescence after short exposure to ultraviolet light (Fig. 3). This autofluorescence was also seen in the Kupffer cells in the latter areas. The developing exposure to the ultraviolet was not necessary, the fluorescence here being seen immediately. The pigment was not doubly refractile. In Tables I and II, comparisons are made to the clinical course and pathologic characteristics of the liver in this case and in that group of chronic idiopathic jaundice cases described by Dubin and Johnson.[3] It will be seen that the two have a great deal in common, both clinically and pathologically. We have no note of the color of this liver at the time of operation, but a slate-gray appearance was a striking feature in the cases of Dubin and Johnson. With the evidence of postnecrotic scarring that was present in the liver, we must consider seriously the possibility that the patient may have had an active hepatitis at one time. We do not feel, with the picture presented in the sections, that we can explain the anemia or the elevated bilirubin levels on the basis of active hepatitis at this time.

DR. FARBER.—But you do not feel that you can avoid a diagnosis of hepatitis because of scarring in the past?

DR. CRAIG.—In the past, yes. In Dubin's cases there was also evidence of fibrosis and atrophy. That is another feature which is similar in his series and the case we have presented here. Drs. Dubin and Johnson have not indicated the etiology in their cases, though they did find groups of cases in the same families with mothers and their children affected.

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Medical Progress

ARACHNIDISM IN CHILDREN

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BLACK widow spider poisoning is not uncommon in the United States, and nearly one thousand cases have been reported in the American literature. Many of these patients have been children but no recent review of this subject has appeared in our pediatric journals. During the past few months I have treated five children below the age of 7 years for arachnidism and I believe they present a somewhat different clinical picture than that seen in the adult.

Spiders belong to the class of arachnida which also includes scorpions, ticks, and mites. The word *arachnidism* might also be used to describe scorpion poisoning or tick paralysis. For this reason some authors prefer to use the term *latrodectism* for black widow spider poisoning. The black widow belongs to the genus Latrodectus, and one or more species are found throughout the world. The female of this species is easily recognized by its shiny black body and the presence of the red hourglasslike markings on the ventral surface of the abdomen. At times, other red or orange markings near the posterior tip of the abdomen may be found. The male is small and lacks the typical markings of the female. The nest or web may be built in numerous locations, but damp, dark places such as those available around lumber piles, barns, trash heaps, and especially "outhouses" seem to be preferred. The webs are sometimes located in garages, under homes, in hollow concrete block walls, under logs, in wooded areas, and very often in our homes.

According to Blair,[1] mating of the *Latrodectus mactans* occurs in the fall or early spring, and a female captured in the fall and isolated from the male may lay fertile eggs in the spring. The eggs are layed in sacs containing about 600 eggs each. These eggs are very poisonous when tested in animals sensitive to spider venom. The eggs may hatch during the summer months in about two weeks, but several moltings are required before a spiderling becomes an adult capable of producing human poisoning. The spiders are cannibalistic, and the spiderlings will eat each other if no food is available. It has been stated that the adult female often kills and eats the male after mating occurs. Thus the name of *black widow* has been given to this spider. There appears to be some doubt[2] that the female actually kills the male. At any rate, the male does not live as long as the female and it is

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the female who is the chief, if not the only, source of spider poisoning in man. Maretic and Stanic[3] in their excellent review of arachnidism as produced by the *Latrodectus tredecimguttatus*, found the male of that species unable to harm the white mouse which is very sensitive to the venom of the female spider.

The venom of the Latrodectus is a thick, translucent, oily fluid believed to be a toxalbumin. It is a hemolysin and also directly stimulates the myoneural junctions and acts on nerves and nerve endings. The venom also seems to have a general toxic effect on the organism. The spider may inject varying amounts of the venom into a victim, depending on the lapse of time since its last feeding. At least in one species the venom is more toxic when the temperature is above 25° C. and less toxic when cooler.[4] The size of the patient is stated to be important since a child would receive more venom per pound of body weight than an adult. I can find little proof that the disease is necessarily more severe in smaller individuals, although fatalities have been reported in both children and adults.[5] There is good evidence that the venoms of some of the species of Latrodectus are similar and produce equal responses in experimental animals. Maretic and Stanic found the antivenom against the bite of the *L. tredecimguttatus* protected animals against the venom of *L. mactans*. Animals produce immunity after being bitten, and this may be true also in man. However, one writer[6] reports a patient bitten twice in forty-one days and had symptoms following each bite.

The clinical picture of arachnidism as caused by the female *L. mactans* has been described and experienced by Blair.[7] This physician allowed himself to be bitten on the hand by the spider. He felt the bite similar to a pinprick, but noted no great local discomfort. Slight redness remained at this site, and within twenty minutes pain was noted along the local lymphatics. Some tenderness was present in the regional lymph nodes. Twenty-five minutes after the injection of the venom he entered what he called the stage of dissemination, during which time he was extremely ill and was in shock. He was gasping, and had severe agonizing muscle pains which continued to increase in intensity for about four hours. He then entered the stage of elimination of the venom during which the muscle pain gradually diminished, but his temperature became elevated, leukocytosis occurred, and evidence of acute toxic nephritis was present. There was edema of his face and ankles, and it was several days before he felt that he had entirely recovered from his illness.

Beasley[8] found no gross pathological findings in an adult male dying as a result of arachnidism. Cisternal puncture done after death revealed a white cell count in the spinal fluid of 210 cells per cubic millimeter. Most of these cells were lymphocytes. Sections of the kidneys studied histologically showed swelling of the epithelial cells of the lining of the tubules and marked extravasation of red blood cells throughout. Microscopic diagnosis was chronic adenitis and acute hemorrhagic nephritis.

Many writers[9] have called attention to the fact that at the site of the bite no pain or reaction may occur. For this reason the history that a spider has bitten the patient may be hard to elicit, and in only 10 per cent of the cases reported has the spider been actually identified as being on the pa-

tient. Halter and Kuzell[10] noted that if the patient was asleep at the time of the spider bite, the immediate pain was not usually sufficient to awaken him.

The location of the bite depends mainly on that portion of the body brought in initial contact with the spider. Since this spider is shy, she usually attacks human beings only when the victim brushes against her, such as the hand of the man threshing wheat, or on the scrotum or penis when the bite occurs in an outhouse. The same sequence of symptoms seems to follow no matter where the venom is injected, although severe cramps in the skeletal muscles may begin nearest this site. Most patients show extreme restlessness, and Frank[11] noted that three-fourths of his military patients with arachnidism cried and showed other evidence of emotional disturbance during the first twenty-four hours of the illness. In practically all patients, the chief complaint is severe abdominal pain which has been said to be about the same intensity as that seen in a ruptured gastric ulcer or a ruptured appendix. Vomiting is common, and many of the patients have complained of a severe headache. A burning sensation of the soles of the feet often occurs during convalescence.

When the patient is examined shortly after the onset of symptoms, he is usually rolling from side to side and has difficulty in remaining still. If the patient is a child, an expiratory grunt may be present and the legs are commonly pulled forward against the abdomen. The abdominal wall may be rigid and tender, but no localized or deep tenderness is found. The abdominal reflexes may be absent, but the tendon reflexes are often hyperactive. The pulse rate may be fast or slow and the body temperature normal or elevated. The blood pressure is often elevated. The white blood count in the peripheral blood may be increased, the urine is reduced in amount and may contain albumin and occult blood. The spinal fluid may be under increased pressure and, except for Beasley's postmortem findings, has not been reported to contain an increased number of white cells.

Morphine,[12] neostigmine methylsulfate with atropine,[13] magnesium sulfate,[14] magnesium or sodium thiosulfate,[15] convalescent serum, lumbar puncture, hot baths, local and intravenous injection of procaine, calcium gluconate,[16] cortisone, hydrocortisone,[17] ACTH, Adrenalin,[18] succinylcholine chloride,[19] d-tubocurarine chloride,[20] antihistamines, specific antivenom,[21] and many other therapeutic agents have been used in the patients with latrodectism. Maretic, with his experience of treating over one hundred cases, felt that morphine and its derivatives, as well as antihistamines, were of little or no value. He found the intravenous injection of 10 c.c. of 0.5 per cent solution of procaine in adults gave transitory but considerable relief of pain. Seven of his patients were treated with cortisone, six were treated with hydrocortisone, and one with ACTH. Some of these patients received relief, but recurrence of symptoms was frequent. The use of hot baths to reduce muscle spasm has been successful in most cases. The use of curare and curarelike substances has been associated with respiratory failure and its use does not seem to be justified in the light of the specific treatment available. Convalescent serum has not proved useful or practical. With the introduction of intravenous calcium gluconate in the treat-

ment of this disease by Gilbert and Stewart,[22] dramatic relief of pain was noted in most of those patients treated. Many physicians feel that the action is specific enough to be used as a diagnostic tool in black widow spider poisoning. The relief of pain, although dramatic, is temporary and the drug will need repeating. Alternate use of calcium gluconate and magnesium sulfate intravenously has proved to be of value. The use of specific Latrodectus antivenom as early as possible in the course of the illness gives excellent and lasting results. The treatment as described by Miller of giving an immediate intravenous injection of calcium gluconate, then skin testing and administering antivenom has given dramatic results in all patients so treated early in the course of the disease.

The antivenom used in this country is supplied in a dry form and when mixed with the water supplied by the manufacturer gives a volume of 2.5 c.c. Since the antivenom is in horse serum, a skin test is necessary to determine possible sensitivity. If the patient is sensitive, desensitization should be attempted only when the administration of antivenom is considered necessary to save life. If the patient is not sensitive, then the contents of one vial is given intramuscularly and may be repeated in a few hours if the patient is not showing signs of improvement. Most victims show a rapid subsiding of symptoms within a few hours, and in contrast to other methods of treatment the effects are usually lasting.

The mortality rate in arachnidism is very low even in children, and most of the patients will recover.

Maretic found DDT unsuitable as an insecticide against the black widow spider and found the best results were obtained with gammabenzene. In his opinion, the control of spiders by insecticides known so far appears rather problematical and expensive. Since most of his patients were bitten while in the wheat fields, this approach would seem impractical. Van Riper,[23] however, found that a 10 per cent solution of DDT in kerosene when sprayed on the web was effective in killing the spider and other spiders were killed when placed on the same web several days later. Most of the children and many adults are bitten near their homes and this spray should be tried if black widow spiders are known to be present. Adults and older children should be taught to identify and avoid the black widow spider. Frank was able to prevent further cases from occurring in his troops by having the men inspect their bedroll each night before retiring.

The following cases illustrate the disease as seen in children.

CASE REPORTS

CASE 1.—This patient was a 6-year-old white female child who was brought to the emergency room at the Gaston Memorial Hospital in November because of abdominal pain following a black widow spider bite. The child was putting on her coat to go to school when she began crying with pain in her right wrist. A black spider fell from the right sleeve of her coat. Within fifteen minutes, the child complained of "pain in her stomach" and within thirty minutes she was crying with severe abdominal pain. She did not vomit and was brought to the hospital about forty minutes after being bitten by the spider. The parents of the child brought the spider with them, and it was identified as a female *L. mactans.*

Physical examination at this time revealed an acutely ill white child who was leaning forward with her hand over her epigastrium. There was an expiratory grunt present and she seemed to be in severe pain. There

was an area of erythema about two inches in diameter on the radial side of her right wrist. The rectal temperature was 99.8° F., and the blood pressure was 110/70. Pulse and respiratory rates were rapid. Pupils were somewhat dilated but responded to light. Examination of the abdomen revealed rigidity of the muscular wall with generalized tenderness. No localized tenderness was present and deep palpation was difficult because of the marked rigidity of the abdominal wall. Intestinal peristalsis was active. Abdominal reflexes were absent but tendon reflexes in the extremities were active and symmetrical. The remaining examination failed to reveal any abnormal findings. The urine analysis was negative and the white blood count in the peripheral blood was 14,150, of which 57 per cent were polymorphonuclear neutrophils, 5 per cent eosinophils, 1 per cent large lymphocytes, 33 per cent small lymphocytes, and 4 per cent monocytes.

Calcium gluconate, 10 c.c. of a 10 per cent solution, was given intravenously immediately with very little relaxation of the muscle spasm. A tourniquet was applied just below the right elbow and an ice pack applied to the site of the bite. A skin test to horse serum was done and 2.5 c.c. of *L. mactans* antivenin (Lyovac*) was given intramuscularly. Seconal, 0.048 Gm., was given by mouth.

Symptoms rapidly diminished, and two hours later all complaints had disappeared. She was discharged home the following day apparently well.

CASE 2.—This patient was a 4-year-old white male child who was brought to the office in September because of severe abdominal pain. He had been playing "under the house" about two hours previously, when he suddenly began crying. He was dressed only in short pants and his chest was bare. The father searched the area where the child had been playing, and found several black spiders. Thirty minutes after the boy had first begun to cry, he complained of a stomach-ache. No nausea or vomiting occurred. When he was seen at the office he was crying and had a marked expiratory grunt. On his chest near the left breast was an erythematous area and the child had been scatching this site. His temperature was 101° F. The pupils were slightly dilated. The abdominal wall was rigid and very tender. There was no localized tenderness and intestinal peristalsis was present. Tendon reflexes were hyperactive and abdominal reflexes were present.

Urine examination was negative. The white blood count was 6,500 with 82 per cent polymorphonuclear leukocytes, 17 per cent small lymphocytes, and 1 per cent monocytes.

Cortisone, 25 mg., was given by mouth, and a warm water enema administered. Two hours after the first dose of cortisone he had had no relief of pain and 2.5 c.c. of *L. mactans* antivenom was given. Three hours later the abdominal pain began to subside and five hours later the child seemed entirely well.

CASE 3.—This 2½-year-old white male child had been well when his mother left him playing in their back yard. He was playing on a concrete block wall which was known to contain the webs of several black widow spiders. When his mother returned at 5:00 P.M., she noticed he was grunting with each breath, and he was leaning forward holding his abdomen. He said that his stomach hurt and this pain seemed to be severe. At 9:00 P.M., his mother brought him to the hospital, where I saw him. He had not vomited.

Physical examination at that time revealed a well-developed, acutely ill white male. The rectal temperature was 100.4° F.; pulse was 120 per minute and respirations were 26 per minute. He was grunting with each expiratory phase of respiration. His pupils were dilated. The abdominal wall was rigid and tenderness was generalized. No deep tenderness was noted, and no unusual masses felt. Careful examination of the skin did not reveal the site of the spider bite.

The white blood count was 21,800 of which 88 per cent were polymorphonu-

*Sharp & Dohme.

clear neutrophils, 2 per cent eosinophils, and 10 per cent small lymphocytes. Urine examination was negative. Chest film and flat plate of the abdomen were normal.

Ten cubic centimeters of a 10 per cent solution solution of calcium gluconate was given intravenously at once, and the child became sleepy. The abdominal muscles relaxed, and the abdominal organ could be palpated without producing pain. His pain, however, returned in an hour and 10 units of ACTH was given intramuscularly. This was continued every four hours, and Chloromycetin plamatate was started. There was no antivenom available at that time.

Despite sedation, he did not sleep much the night of admission to the hospital. The grunting respirations and tense abdominal wall were still present the following morning. This continued for twenty-four hours and gradually diminished in intensity. He seemed entirely well by the third hospital day, and was discharged home. Surgical consultation on second hospital day was obtained, and the surgeon did not believe an acute abdominal infection was present.

The day following the onset of this illness, the child's father found twenty black widow spiders in the concrete block wall where the child had been playing, and found one such spider in their home.

CASE 4.—This 3-year-old white male child had been playing on the banks of the Catawba River, when he suddenly cried out in pain. He ran to his mother and shortly thereafter complained of a "stomach-ache." Within a few minutes he was screaming with abdominal pain. He did not seem to have a fever at that time. His mother called me and I asked her to look for spiders in the area where the child had been. She found several spiders, but none of these were black widows.

I saw the child about one hour after the onset of symptoms. He was well nourished, but appeared pale and in acute pain. There was a loud expiratory grunt present and he held his hand on his abdomen. The abdominal wall was rigid and tender. No masses or localized tenderness was noted. Intestinal peristalsis was active. The skin was clear of rashes, and the site of the spider bite was not found. The rectal temperature was 98.8° F.

The white blood count was 12,500 of which 72 per cent were polymorphonuclear leukocytes, 27 per cent small lymphocytes, and 1 per cent monocytes. The urine was negative.

Ten cubic centimeters of calcium gluconate was given intravenously, at which time the skin became flushed and he fell asleep.

The abdominal wall relaxed, and no tenderness was present on deep palpation. Twenty-five units of ACTH was given intramuscularly and was repeated every six hours. About three hours after admission, most of the abdominal tenderness had disappeared and the respiratory grunt was gone. No antivenom was available for this child, but he did very well nevertheless, and was discharged home the day after admission.

CASE 5.—This 3-year-old white female child was playing in the garage attached to her home when she suddenly cried out to her mother to come and get a bug off her neck. The mother found a black spider in the child's hair and two puncture wounds on the child's neck. The mother called me at once, and I saw the child within thirty minutes after she had been bitten. I identified the spider as a female *L. mactans*.

The little girl was already complaining of abdominal pain and a headache. She had a slight expiratory grunt and vomited once while being examined. The rectal temperature was 100° F. and her blood pressure 95/60. The abdominal pain and rigidity of the abdominal wall became more marked during the next few minutes. Generalized abdominal tenderness was severe but no localized tenderness was present. Intestinal peristalsis was active. There was no local pain or reaction around the two small puncture wounds on the necks, and if the mother had not shown me the location of the bites, I do not think I would have found them.

Calcium gluconate was given intravenously with very little relief of pain. *L. mactans* antivenom (Lyovac), 2.5 c.c., was given after skin testing. Fifty units of ACTH was given intramuscularly and then 25 units every six hours. An ice pack was placed on her neck. She vomited several times after being admitted to the hospital, but within six hours after treatment had begun she seemed well. She had no symptoms the next day and was allowed to return home.

find the spider on the victim even when the patient is an adult, and the history of the bite being noted by the child would be elicited in even a smaller number of cases.

Abdominal pain with rigidity of the abdominal wall was present in all five patients treated. A finding which seems to occur more frequently in children than in adults is the expiratory grunt which seems to be the result of

TABLE I

CASE NO.	MONTH ILLNESS OCCURRED	AGE (YEARS)	SEX	CHIEF COMPLAINT	GRUNTING RESPIRATIONS	TENDER AND RIGID ABDOMINAL WALL	ADMISSION WHITE BLOOD COUNT	ADMISSION RECTAL TEMPERATURE (F)	TREATMENT
1.	Nov.	6	F	Spider bite Abdominal pain	Yes	Yes	14,150	99.8°	Calcium gluconate, antivenom, Seconal
2.	Sept.	4	M	Abdominal pain	Yes	Yes	6,500	101°	Cortisone, antivenom
3.	Oct.	2½	M	Grunting Abdominal pain	Yes	Yes	21,800	100.4°	Calcium gluconate, ACTH, Chloromycetin
4.	July	3½	M	Abdominal pain	Yes	Yes	12,500	98.8°	Calcium gluconate, ACTH, Seconal
5.	June	3½	F	Spider bite Headache	Yes	Yes	Not done	100°	ACTH, antivenom, Seconal, calcium gluconate

DISCUSSION

I believe that each of the cases (summarized in Table I) presented is an example of arachnidism. Although the spider was found on only two of the children, one of the other patients (Case 2) showed an area of erythema believed to be caused by an insect bite, and he responded well to antivenom. The father of the child in Case 3 found many black widow spiders on the concrete block wall where the child had been playing when he became ill. As mentioned previously, it is unusual to

an effort not to relax or move the abdominal wall. The white blood count was elevated in three of the four children tested and most of the white cells were polymorphonuclear neutrophils. The rectal temperature was elevated during the acute phase of the illness in four children.

The abdominal pain subsided somewhat in all cases after calcium gluconate was given and was dramatic in its relief of pain in three patients. Best results with treatment seemed to occur when both calcium gluconate and anti-

venom were used. However, a rapid response to treatment with ACTH was noted in at least one patient (Case 4). Four of the children seemed well within six hours after treatment was started, and the other patient (Case 3) was not entirely well until forty-eight hours after the onset of symptoms.

Acute appendicitis and peritonitis can give a clinical picture quite similar to that seen in these children. The lack of localized abdominal pain, the absence of deep tenderness on palpation, as well as the relaxation of the abdominal wall after the administration of calcium gluconate will help the examiner to make the diagnosis of arachnidism. Children with intussusception most often have abdominal pain which is more intermittant than the pain produced by spider venom. The diagnosis of arachnidism should be considered in every patient who has an acute onset of abdominal pain.

SUMMARY

1. The subject of black widow spider poisoning has been reviewed, and five cases of this illness as it occurs in children have been presented.

2. The expiratory grunt was a constant finding in these children as well as abdominal pain and rigidity of the abdominal wall.

3. Calcium gluconate and *Latrodectus mactans* antivenom were found to be agents most useful in the treatment of this illness.

4. Specific antivenom is supplied in a dry form which is stable for several years. Every doctor who might be called upon to treat a patient with arachnidism should be certain that the antivenom is readily available in his community.

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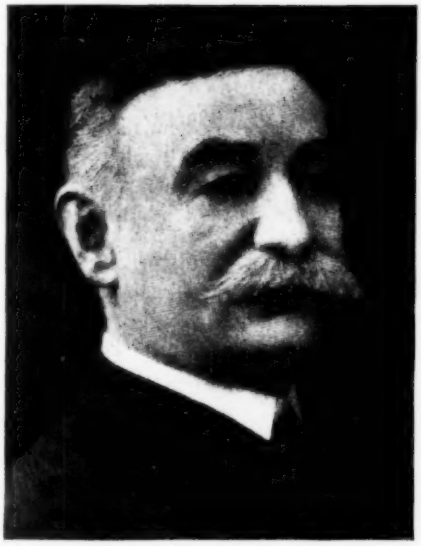
Pediatric Profiles

Thomas Morgan Rotch

(1849-1914)



IN THE early days of pediatrics in the United States, when the pediatrician not infrequently was rather condescendingly referred to by his colleagues as a "baby feeder," infant feeding was dominated by what was known as the "percentage method." The originator and high priest of the method was the pioneer Boston pediatrician Thomas Morgan Rotch, who was the first to hold the chair of pediatrics at Harvard, and whose name is attached to the professorship today. How much, if at all, he was influenced by the earlier writings of the German pediatrician Biedert, whose rather similar ideas never attracted much following in Germany, is unknown. It was Rotch's idea and teaching that by modifying the percentage of fat, carbohydrate, and protein in cow's milk to make it percentage-wise similar to mother's milk, an ideal food for the artificial feeding of infants would be obtained. Moreover, by further modifying the percentage of fat or protein, a satisfactory food could be prepared for the delicate infant with "feeding difficulties," whose troubles were attributed to his inability to digest fat or protein, as the case might be in the opinion of the physician. It was looked upon as the first "scientific approach" to infant feeding, and rapidly became widely accepted and used in practice. Until roughly about 1915 it was the method of infant feeding taught in most medical schools, although there were some dissenters such as Abraham Jacobi. It brought fame to Rotch, and he became an outstanding figure in the development of pediatrics at this period, along with Jacobi and Holt. Dr. Holt became an ardent follower of Rotch in this respect and a powerful protagonist for the method.*

*Editor's Comment: The "percentage method" will be discussed in detail in the Profile of Dr. L. Emmett Holt, by Edwards Park, in a later issue.

Thomas Morgan Rotch was born in Philadelphia December 9, 1849. His father came from an old whaling family in New Bedford, Massachusetts, so it was natural that Rotch should return to New England for his college and medical school education at Harvard. He received his A.B. in 1870 and his M.D. in 1874. He was medical house officer at the Massachusetts General Hospital, 1873-1874, and then, following the accepted custom of the time, went abroad for two years, studying in Berlin, Heidelberg, and Vienna. The *Dictionary of American Biography* says that upon his return to this country "he began at once the practice of Pediatrics, a specialty unknown at that time; no other physician in the United States had yet attempted to limit his practice to patients in the first two years of life." Actually, however, he was preceded by others who practiced pediatries. One of the earliest of these was Abraham Jacobi, who was well known in New York as a pediatrician in 1857, and became the first professor of the diseases of children in this country at the New York Medical College in 1860. Dr. Rotch was the pioneer pediatrician in Boston, concentrating his work on those years of life that had the highest death rate. In 1881 he established the West End Nursery in Boston with Dr. H. C. Haven and became its director in 1894. He commenced teaching pediatries as early as 1878 in the Harvard Medical School, and in 1903 was appointed to the newly created professorship of pediatries. Very early he was appointed to Boston Dispensary, and shortly his interests became identified with the Infants' Hospital and the Boston Children's Hospital.

He put his heart into developing and building the Infants' Hospital which was renamed the Thomas Morgan Rotch, Jr. Memorial Hospital in 1903 but shortened in 1907 to Infants' Hospital. In 1913 it was transferred to the grounds of the Children's Hospital of which it is now an integral part. He had planned the building, and one of his last activities was to select its furnishings and equipment. It was to be opened March 3, 1914. Dr. Rotch was taken ill shortly before and was unable to be present. He died a few days later, on March 9, and his funeral services were held in the lobby of the new building.

Dr. Rotch was the first president of the New England Pediatric Society, a founder member of the American Pediatric Society in 1888, and President in 1891, belonged to the Association of American Physicians, the Massachusetts Medical Society, and was Fellow of the Association for the Advancement of Science.

Dr. Rotch had a sad life: in 1902 he lost his only son who died shortly after his graduation from Harvard. He had an invalid wife who was a great care to him, and during his last years he was handicapped financially.

Rotch was a short, stocky man, whose face was adorned by a large mustache, and his voice was high pitched. The shortness evidently was a trial to him as he wore an extra lift in the heels of his shoes to make him appear taller. He was something of a "dandy," and made considerable impression on the younger members of the staff by driving up to the hospital in a snappy open buggy, with a coachman and a beautifully equipped horse. Those of the men still living

who held a very junior place in the "Rotch era" recall he had a pleasant personality and was kindly toward them. John Lovett Morse, who succeeded him at Harvard, was a staunch, loyal supporter and disciple. In fact he was so devoted to Rotch that he insisted the "percentage method" be taught to the medical students for a number of years after it had been generally discarded. As a result the younger men had to teach this method of infant feeding despite the fact they did not use it in their own work. As one once remarked when being chaffed about it by his friends from other schools, "otherwise I'd lose my place on the staff." The influence of Rotch dominated for many years.

Dr. Rotch was not what might be termed a popular man professionally, or with many pediatricians in other cities, although the importance of his pediatric work was clearly recognized and acknowledged. At one time there was considerable criticism of him among the members of the American Pediatric Society over an incident in which it was felt that he had not stood by and come to the aid of one of his assistants as he should have done, at a time when the support of his prestige was sorely needed and indicated. One of his assistants, Dr. Arthur W. Wentworth, regarded as a very fine person and a careful investigator, was studying the use of lumbar puncture as a method of diagnosis (something new at that time), and in a report before the Society in 1896 made the unfortunate statement that he had performed lumbar puncture on normal children "to show that the withdrawal of fluid from the subarachnoid space by means of lumbar puncture is a harmless procedure." At that time there was a popular national magazine which was fanatically tirading against vivisection. The report of this work was seized upon and much ado was made, criticizing the medical profession. Rotch, who had full knowledge of the work, and tacitly at least must have approved of it, never, for some unexplained reason, openly came to the defense of the work or to the support of his assistant. So much furor was raised by the attack in the magazine that Wentworth lost his hospital position and a promising career was ruined. Interestingly enough, he gave up the practice of medicine and went abroad to live, where he became a successful painter.

There is another matter over which criticism of Rotch has been handed down for many years. This is the important work, pioneer in nature, on the development of the epiphyses at different age levels in order to establish the difference between anatomic and chronologic age, which was fully developed later by Todd and by Greulich in their studies at the Brush Foundation in Cleveland. This early work at Boston was brought out in a book with Rotch as the author. He was not a roentgenologist although much interested in the subject, and, according to one of his associates at that time, always depended on an x-ray man for the interpretation of the plates. No credit was given to the young roentgenologist, Dr. Arial W. George, who actually made the technical studies, and his only recompense was in the nature of a monetary one from Rotch. Whether this was an accepted and customary arrangement at that time

is difficult to determine, but it has been talked about many times in discussion of Rotch. In fairness to Rotch it may be said that at this time it was not unusual for certain German professors who were his teachers while there to take full credit for the work of their assistants. It can be argued that Rotch did nothing unethical in relation to the times, and gave generous payment in light of the purchasing value of the dollar fifty years ago.

His textbook of pediatries, *Prognosis, Diagnosis, and Treatment of the Disease of Children*, was contemporary with Holt's early textbook, and went through several editions. The discussions of some of the topics were written by his associates, among them Charles Hunter Dunn in particular, although no credit was given as would have been done today. Rotch apparently was not too familiar with these sections. One of his early assistants amusingly recalls how at times in his discussions, when a case or a disease involving one of the topics came up, he would stop and ask him to read to the class "what he had said about it in the book." He was regarded as an excellent teacher.

There is no question as to the important place and influence of Rotch in the early development of pediatries in the United States. He lived at a time when he had to fight for its recognition, and he made a valiant and successful fight against great odds. He not only recognized the necessity for dispensary services and hospital beds for infants and children, but put untiring effort into their development in Boston. He was most active in a crusade for clean milk, which he emphasized, above all, for the feeding of infants, and which was the most urgent and important problem at that time for what later became to be known as preventive pediatries. Through his pioneer work as a teacher of pediatries in the Harvard Medical School, and through his textbook, he exerted an influence that extended far beyond his own community. From the standpoint of pediatric history the "percentage method" of infant feeding which he developed was his most important contribution, despite the fact that this "first scientific approach" was later discarded as based on concepts which were no longer considered scientific. Nevertheless it dominated pediatric thinking as well as teaching and practice for many years. He was one of the most important pioneer pediatricians in this country, and, in retrospect, was a man in some ways years ahead of the times in which he lived.

Fritz B. Talbot.

Comments on Current Literature

HEPATITIS IN INFECTIOUS MONONUCLEOSIS

THE PROTEAN manifestations of infectious mononucleosis, especially in children, make this disease a diagnostic possibility to be considered in all conditions presenting respiratory manifestations such as throat infections, "colds," influenza-like disease, and the common contagious diseases. Recent reports have emphasized the more serious aspects of infectious mononucleosis. These have included hepatic involvement; acute pericarditis and involvement of the heart; hemolytic anemia, severe central nervous system involvement with coma and personality change, which was followed in one recorded instance, by a temporary convulsive disorder; pleural effusion with infiltration of the pleura by mononuclear cells and lymphocytes; follicular conjunctivitis with periorbital edema, and, in some cases, optic neuritis.

The diagnosis of infectious mononucleosis should be considered in any patient with mild transient jaundice, since hepatic dysfunction is known to occur in infectious mononucleosis in children.[1] Confusion with infectious hepatitis is a possibility, especially since lymphocytosis not infrequently accompanies infectious hepatitis. Likewise, as in the case of infectious hepatitis, involvement of the liver may occur in patients with infectious mononucleosis in the absence of clinical jaundice.

More recently Hoagland and McCluskey[2, 3] have presented observations which "indicate that liver involvement is not a complication, but a regularly occurring feature of mononucleosis."[3] This, they state, is not surprising "since the cause of mononucleosis appears to stimulate proliferation of lymphocytes, and the mesenchymal cells of the liver are potential precursors of lymphocytes."[3] The primary purpose of their recent investigations, carried on at a United States Army Hospital, was to determine whether histologic studies would support the impression based on clinical experience[4] that the hepatitis of infectious mononucleosis is mild, and need not preclude reasonable ambulation of the patient. The secondary purpose of these authors was a study of needle biopsies in patients with mononucleosis, with a view to comparing both the clinical manifestations and, so far as is possible, the histopathology of infectious mononucleosis and infectious hepatitis. Lymphocytic infiltration of many organs has been described in autopsy reports in fatal cases of mononucleosis; the outstanding change seen in the liver seems to be the presence of many mononuclear cells in the portal areas, and throughout the lobules within sinuses. In general, neutrophils are seen rarely, and evidence of liver cell damage is minimal.

In contrast to the typical patient with infectious hepatitis, who tends to seek medical advice because of signs of jaundice, the typical patient with infectious mononucleosis seeks medical attention because of fever, chilliness, malaise, and often sore throat. When first seen, patients with mononucleosis are not jaundiced, as a rule, and only about 5 per cent of these patients appear jaundiced at any time during the illness. The jaundice is rarely intense, and usually disappears within about three weeks. Liver enlargement is present in only about 15 per cent, is

not marked, and liver tenderness is minimal. The authors noted obvious jaundice in only four of a total of 100 cases of infectious mononucleosis proved serologically.[4] The cephalin flocculation test is usually positive in mononucleosis; in nonjaundiced patients, the serum bilirubin level is ordinarily less than 1.0 mg. per 100 c.c.; in jaundiced patients it may be of the order of 8.0 mg. per 100 c.c. These laboratory and clinical findings reported by Hoagland and McCluskey are in agreement with those recorded by other investigators.

Since the laboratory findings in infectious mononucleosis are not particularly revealing, and are not pathognomonic of liver damage, the authors turned to histopathology as an objective means of ascertaining the nature and the degree of hepatic involvement. Needle biopsies of the liver were performed in seven nonicteric and in three icteric patients with serologically proved infectious mononucleosis. The pathologic changes were similar in all ten cases, the most striking change being the presence of large numbers of mononuclear cells in the portal areas and throughout the lobules within sinuses. "Many of the cells had the appearance of typical small lymphocytes, but there were also larger cells with slightly vesicular nuclei and more abundant cytoplasm, which probably correspond to the atypical lymphocytes seen in the peripheral blood."[3] In four patients, the portal exudate contained small numbers of eosinophils. Few neutrophils and no plasma cells were observed. In general, liver cell damage was minimal. However, in eight of the ten patients studied small accumulations of mononuclear cells and lymphocytes occurred at random within the lobule. The number of such foci observed was small in every case, and, when present, the foci were associated with necrosis of few hepatic cells. In contrast to the more extensive parenchymal damage which characterizes infectious hepatitis, it would seem that little hepatic cell involvement occurs in mononucleosis.

On the basis of clinical experience and laboratory findings on patients with infectious mononucleosis, whose follow-up periods varied from two to three years, the authors conclude that the hepatitis associated with mononucleosis is mild, and that rigid management and prolonged bed rest are not essential. Patients in their series who were allowed to resume regular activities shortly after becoming afebrile, or as soon as they were able clinically, showed no ill effects and no residual damage over a relatively long observation period.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

In an epidemic of staphylococcal infections in the newborn nurseries at the Ohio State University Hospital, a single strain of *Staphylococcus pyogenes*, phage type 42B/47C/44A/52, was found to be responsible for all lesions. A report of this epidemic is to be published in *Pediatrics* (Shaffer, T. E., Baldwin, J. N., Rheins, M. S., Sylvester, R. L., Jr.: Staphylococcal Infections in Newborn Infants: I. A Study of an Epidemic Among Infants and Nursing Mothers).

Recently we have had opportunities to study organisms responsible for similar epidemics among newborn infants and nursing mothers in Portsmouth and Lancaster, Ohio; Lepeer, Michigan; Seattle, Washington; Hartford, Wisconsin, and Philadelphia, Pennsylvania, and have found that in every instance phage type 42B/47C/44A/52 was responsible. This suggests that epidemics of this sort in newborn nurseries may be a disease entity caused by a single strain of *Staph. pyogenes*.

In all but one instance the strains from the epidemics mentioned above also demonstrated an identical pattern of antibiotic sensitivity.

Studies of this problem are being continued by the Departments of Pediatrics and Bacteriology at the Ohio State University. We would appreciate receiving cultures from pustular lesions of infants or purulent breast lesions of mothers obtained during nursery outbreaks of epidemic proportions. Reports of bacteriologic findings will be promptly transmitted.

Cultures and communications should be addressed to the Phage Typing Laboratory, Department of Bacteriology, Ohio State University, Columbus 10, Ohio.

THOMAS E. SHAFFER, M.D.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Atlantic City, N. J., May 3, 4, and 5, 1956.

Dr. Hreidar Agustsson, U. S. Army Hospital, Aberdeen Proving Ground, Md.

Dr. Robert Earle Appleby, 39 Danbury Road, Wilton, Conn.

Dr. Albert Sidney Beasley, 115 East State St., Westport, Conn.

Dr. Frederick B. Becker, U. S. Naval Hospital, Portsmouth, Va.

Dr. Doris Ruth Rubin Bennett, 462½ Highland Ave., Malden, Mass.

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Dr. Pierre Aymar Lechaux, 3704 P St. N.W., Washington, D. C.

Dr. J. Frederick Lee, 90 Dayton Ave., Greenwich, Conn.

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Dr. Ralph Henry Leyrer, 707 Elmwood Ave., Hamilton, Ohio.

Dr. David A. Lockhart, Ardsley Rd., Concord, N. C.

Dr. Harry V. Lomant, 107 Pennsylvania Ave., Mt. Vernon, N. Y.

Dr. Margaret S. Lyman, University Hospitals, Iowa City, Iowa.

Dr. Anna (nee Turyesyn) Mitus, Children's Medical Center, 300 Longwood Ave., Boston, Mass.

Dr. Harold M. Nitowsky, Sinai Hospital, Baltimore 5, Md.

Dr. William Gorgas Palfrey, 4813 Convention St., Baton Rouge, La.

Dr. M. Gilbert Pascoe, 194 Dufferin Ave., Brantford, Ontario, Canada.

Dr. Robert A. Pastel, 203 No. Main St., No. Syracuse, N. Y.

Dr. Anthony S. Raimo, 10 Wilsey Square, Ridgewood, N. J.

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Dr. Mary Retsina-Babakitis, 8058 So. Burnham, Chicago 17, Ill.

Dr. Lawrence Sidney Ross, 1369 New York Ave., Huntington Station, N. Y.

Dr. Herbert B. Rothschild, 1520 Louisiana Ave., New Orleans, La.

Dr. Lewis James Rutledge, Charity Hospital of La., New Orleans 12, La.

Dr. Robert T. Sceery, 109 No. Main Street, Cohasset, Mass.

Dr. Edward Manning Sears, 35 Binney St., Boston, Mass.

Dr. Fredrika P. Smith, 264 Elm St., Northampton, Mass.

Dr. Arthur Alan Stamler, Jefferson Medical Center, 6431 Airline Highway, New Orleans 20, La.

Dr. Shirley H. Stone, 8 Gramercy Park, New York 3, N. Y.

Dr. Charles Walker Streamer, 4200 East Ninth Ave., Denver 20, Colo.

Dr. David T. Tayloe, 209 N. Washington St., Washington, N. C.

Dr. Mario Vigliani, Box 518, USAF Hospital, Sampson AFB, Geneva, N. Y.

Dr. George W. Ward, 1512 West Girard Ave., Philadelphia, Pa.

Dr. Robert Weir Watson, Jr., 311 South Floral, Visalia, Calif.

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Dr. Allen Stanley Weed, 18-B Eagan Ave., Langley AFB, Va.

Dr. Helen S. Whaley, 62 Summit Ave., Brookline, Mass.
Dr. David W. Wood, 346 W. Baltimore Ave., Media, Pa.
Dr. Louis Culberson Zang, Jr., 601 W. 4th St., Odessa, Texas.
Dr. Joseph Ziegler, 8 West Union St., Burlington, N. J.
Dr. Joseph I. Zuckerman, 1430 Tulane Ave., New Orleans 12, La.

Note: The oral examination which was originally scheduled for San Francisco, Calif., on Dec. 7, 8, and 9, 1956, will now be held in St. Louis, Mo., on the same dates.

The following were elected to active membership:

Dr. Forrest H. Adams, Los Angeles, Calif.
Dr. James Bosma, Salt Lake City, Utah.
Dr. Ronald L. Denton, Montreal, Canada.
Dr. Paul A. di Sant'Agnese, New York, N. Y.
Dr. James N. Etteldorf, Memphis, Tenn.
Dr. Lytt I. Gardner, Syracuse, N. Y.
Dr. T. Campbell Goodwin, Cooperstown, N. Y.
Dr. Weston M. Kelsey, Winston-Salem, N. C.
Dr. Robert Klein, Pittsburgh, Pa.
Dr. Harry Medovy, Winnipeg, Manitoba.
Dr. Ralph E. Moloshok, New York, N. Y.
Dr. Theodore C. Panos, Galveston, Texas.
Dr. Helmut P. Seckel, Chicago, Ill.
Dr. Frederick N. Silverman, Cincinnatti, Ohio.

At the Sixty-sixth Annual Meeting of the **American Pediatric Society** at Buck Hill Falls, May 9, the following officers were elected for 1956-1957:

President, Dr. Daniel C. Darrow.
Vice-President, Dr. Samuel Z. Levine.
Secretary-Treasurer, Dr. Aims C. McGuinness.
Recorder-Editor, Dr. Stewart H. Clifford.
Member of the Council: For a seven-year term, Dr. F. Howell Wright.

The 1957 meeting will be held at the La Playa Hotel, Carmel, Calif., beginning Monday afternoon, June 17.

A new fellowship program designed to provide an opportunity for pediatricians to prepare for an academic career in pediatric education with an emphasis on the social science and psychological aspects of pediatrics will be initiated by the **Department of Pediatrics of State University of New York Medical Center in Syracuse** in the fall of 1956. The program is intended to provide a background for research and teaching in the cultural, social and psychological aspects of pediatrics. Ample opportunity for continuing experience in pediatric practice and teaching will be available. The program provides for a three-year training period with the appointment of one Fellow each year, so that a maximum of three Fellows will be in training at one time. Candidates should have completed their residency training in pediatrics. This program is being supported by a grant from the Commonwealth Fund. Inquiries should be addressed to: Dr. Julius B. Richmond, Chairman and Professor, Department of Pediatrics, State University College of Medicine, Syracuse 10, N. Y.

The **Institutes for Physicians and Nurses in the Care of Premature Infants** at the New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, will begin their eighth year of operation in the fall of 1956. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers, and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1956-1957 year are definitely scheduled to start on the following dates: Sept. 17, 1956; Nov. 5, 1956; Jan. 14, 1957. In addition, if the number of applicants is sufficient to warrant it fourth and fifth Institutes will be scheduled beginning: March 11, 1957; and early in May, 1957. Early application for these Institutes is essential since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 East 68th St., New York 21, N. Y.

Books

Behaviour Problems of Children. J. C. Marfatia, M.B.B.S., D.P.M., Bombay, 1956, The Association of Pediatricians of India, 159 pages. Price Rs. 6/4.

While there is nothing particularly new in this discussion of behavior problems, it is of unusual interest as the first book of its kind to come out of India, and further that it is sponsored by the pediatric association of India. The writing is concise and clear, and free from psychiatric jargon. The author has full knowledge of the advances and developments in child psychiatry that have occurred in many countries in recent years, and has succeeded in his objective.

Maternal Emotions. Niles Newton, Ph.D., New York, 1955, Paul B. Hoeber, Inc., 140 pages. Price $3.00.

While the studies of Mrs. Newton of the department of obstetrics at the University of Pennsylvania are of more importance to the obstetrician than the pediatrician, this attempt to study objectively the influences and effects of maternal emotions will be found of considerable interest. The author makes no startling claims for the results of the studies, but rather that certain findings indicate a need for further study. Thus, for example, eight specific differences were found between a group of women who were anxious to breast feed their babies compared with a group who expressed little desire to nurse.

Prenatal and Paranatal Factors in the Development of Childhood Behavior Disorders. Martha E. Rogers, Sc.D., Abraham M. Lilienfeld, M.D., and Benjamin Pasamanick, M.D., Baltimore, 1955, Johns Hopkins University, 155 pages.

A report of a study, including statistical data, carried out in 1953-1954 in the School of Hygiene and Public Health, in an attempt to throw light on the question of whether or not a relationship exists between behavior problems in childhood and disorders occurring in pregnancy and at the time of the birth of the child. Although the results are rather inconclusive, the authors found that a history of a toxemia of pregnancy was more frequent for the case group (471 children) than for the control group (359 children). The authors feel that their findings justify the inclusion of prenatal and paranatal factors in considering the causes of behavior disorders in children, and that their findings indicate a need for further study of the question.

The Human Adrenal Cortex. Edited by G. E. W. Wolstenholme and Margaret P. Cameron, Boston, 1955, Little, Brown and Co., 653 pages. Price $10.00.

Vol. VIII of the colloquia on endocrinology of the Ciba Foundation. Proceedings of two symposia held in 1954. The first, under the chairmanship of Dr. Gregory Pincus, was a discussion of the histological and biochemical aspects of corticomedullary relationships. The second, under the chairmanship of Dr. George W. Thorn, was a consideration of the physiological and pathological relationship. The volume contains the thirty-five papers presented at the symposia, together with the discussions.

Psychopathology of Childhood. Edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D., New York, 1955, Grune & Stratton, 303 pages. Price $6.00.

The Proceedings of the meeting of the American Psychopathological Association held in June, 1954. Contains sixteen papers presented at the meeting on such subjects as the psychopathology of mental deficiency in children, trends in child development, and adolescent frustrations and evasions.

Our Blind Children. Growing and Learning With Them. Berthold Lowenfeld, Ph.D., Springfield, Ill., 1956, Charles C Thomas, Publisher, 205 pages. Price $5.50.

This book by the Superintendent of the California School for the Blind is intended primarily for parents with a blind child. It is particularly timely because of the recent increase in the incidence of blindness due to retrolental fibroplasia. The book discusses in an understanding and sympathetic way the problems that are encountered as the blind child grows up, particularly the problems in education. It is a book that the physician should keep in mind to recommend to parents who have to face the problem.

Poliomyelitis. Papers and Discussions Presented at the Third International Poliomyelitis Conference, Philadelphia, 1955, J. B. Lippincott Co., 565 pages. Price $7.50.

A volume containing the papers and discussions presented at the Congress in Rome in 1954. It is well edited and printed and will be useful to those interested in poliomyelitis. The scope is broad and includes the clinical orthopedic and rehabilitation aspects as well as the immunological.

Psychopathology of Children With Organic Brain Disease. Lauretta Bender, M.D., Springfield, Ill., 1956, Charles C Thomas, Publisher, 151 pages. Price $5.50.

The fourth book of a group based on the studies and experience at the Bellevue Children's Service where the author is senior psychiatrist of the Service. The present volume deals with the personality problems of children with organic brain disease due to such disorders as congenital cerebral lesion, encephalitis, and head injuries.

Die Klinik der congenitalen Angiocardiopathien im Saüglings- und Kleinkindesalter. Privatdozent W. Heck, Stuttgart, 1955, Gustav Fischer Verlag, 128 pages. Price 26.50 D.M.

A short clinical monograph on the diagnosis of the various types of congenital cardiac lesions studied at a special clinic in Göttingen.

Caring for the Sick Child at Home. Marion Lowndes, Philadelphia, 1955, The Westminster Press, 157 pages. Price $3.00.

A text for mothers, containing helpful advice on the care of a sick child, and methods for keeping the child more comfortable and contented.

Handbook of Toxicology. Vol. I. Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals. Edited by William S. Spector, Philadelphia, 1956, W. B. Saunders Co.

A technical compilation prepared under the direction of the committee on the Handbook of Biological Data of the National Research Council.

A Course in Practical Therapeutics. M. E. Rehfuss, M.D., and Alison Howe Price, M.D., Baltimore, 1956, Williams & Wilkins Co., 973 pages. Price $15.00.

A third edition. Many changes in treatment have taken place since the second edition published in 1950, due, in particular, to new antibiotics.

A Modern Pilgrim's Progress for Diabetics. Garfield G. Duncan, M.D., Philadelphia, 1956, W. B. Saunders Co., 222 pages.

A pocket-sized discussion of diabetes for the diabetics.

Mongolism. A Symposium. Association for the Help of Retarded Children, New York, 50 pages. Price $1.00.

A collection of papers by several authors covering the various aspects of problems of mongolism.

Electrocardiography. Fundamentals and Clinical Application. Louis Wolff, M.D., Philadelphia, 1956, W. B. Saunders Co., 342 pages. Price $7.00.

A second edition.

Clinical Recognition and Management of Disturbances of Body Fluids. John H. Bland, M.D., Philadelphia, 1956, W. B. Saunders Co., 522 pages. Price $11.50.

A second edition.

Editor's Column

THE RISE AND FALL OF RETROLENTAL FIBROPLASIA

WE DOUBT if there has been a more dramatic episode in the history of medicine than the story of retrolental fibroplasia. Unknown as a disease until 1942, within a decade it became the leading cause of blindness in childhood. This rapid increase was coincident with and paralleled a campaign to reduce the high death rate of premature infants, in which emphasis was placed on the feeding and vitamin intake and on the use of incubators to which oxygen was supplied. Then RLF appeared with a rapidly climbing incidence. A number of suggested causes were investigated, only to be discarded.

Ryan of Australia was probably the first to link the incubator with the disease. In a communication published in 1952 he noted that it was unknown in a Melbourne hospital prior to the use of an "efficient oxygen cot." In the fall of 1950 the cot was discarded except for babies actually cyanosed, and no further cases were observed. Late in 1951 a preliminary report was published by Szewecyk, followed by a more detailed report in March, 1952, of his observations on the Premature Unit of a hospital in East St. Louis, Illinois. His contention was that RLF may be induced by exposing a premature infant to a high oxygen concentration. The idea was received with considerable skepticism, and some of the observations which Szewecyk reported, as the "rapid withdrawal" of oxygen being a factor, and as to the "reversibility" of the condition, are still controversial. Not, however, the etiological relationship of oxygen, as experimental and clinical studies soon confirmed the important role played by a high oxygen concentration in the development of the disease. This culminated in a comparative study in eighteen hospitals whose report published in January, 1955, clearly established an etiological relationship between oxygen and RLF. Even before the report appeared evidence that Szewecyk's contention was correct was accumulating so rapidly that the use of oxygen was being sharply limited in many premature nurseries, particularly oxygen in high concentration. By 1953 a decrease in the incidence of the disease was being noted when the use of oxygen was limited. Thus what was advocated and looked upon as good pediatric practice had to be rapidly discarded.

In a recent May issue of the *New York State Journal of Medicine,* an epidemiological study, *The Rise and Fall of Retrolental Fibroplasia in New York State* by Yankauer, Jacobziner, and Schneider of the New York State and City Departments of Health statistically confirms the etiological relationship of oxygen, in that it shows

the effect on the incidence of the disease when the amount and concentration is strictly limited. The authors and publishers have kindly given us permission to reproduce a graph (Fig. 1) from the report.

The graph plots two curves: one for the cases reported in the year of birth, and the other for cases reported within one year after birth, as the diagnosis often is not made until a number of months after birth. Both curves show a sharp and steadily mounting rise from 1947 to 1953, and then an abrupt decline in the number of cases from 1953 to 1955. We do not recall any other graph showing such an abrupt decline in the incidence of a specific disease. The number reported "in the year of birth" fell from a peak of fifty-two in 1953 to three in 1955; the cases reported "one year after birth" fell from over ninety in 1952 to twenty-eight in 1954.

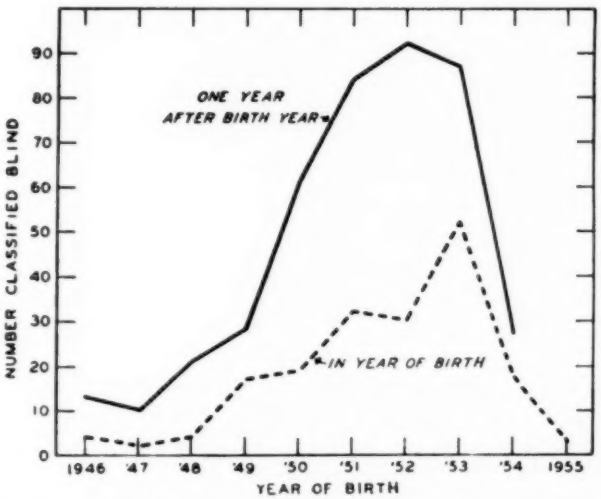

Fig. 1.—Number of cases of retrolental fibroplasia in New York State by year of birth and year classified blind, 1946 to 1955.

How this was brought about was as follows. In 1953 the New York City Department of Health, months before the report of the cooperative study, feeling that the evidence at hand of the relationship between oxygen and RLF was fairly conclusive, recommended the reduction of the oxygen concentration to newborn infants. A joint committee representing obstetrics, pediatrics, and ophthalmology drew up definite recommendations to be followed in the newborn nurseries. In the fall of 1954 the State Department of Health took similar action. Whenever a case was reported a detailed follow-up investigation was made by a representative of the Health Department. The result is shown in the graph.

The exact role of oxygen is still not clear. RLF is a developmental disease and the question remains whether oxygen acts in a direct way, or in

some way as a "trigger mechanism." Regardless, what is important is that this "man-made disease," brought about with the best of intentions, is preventable by the strict limitation of the amount and concentration of oxygen supplied the premature infant in an incubator.

When the JOURNAL in May, 1952, called Szewczyk's ideas and Ryan's observations to the attention of pediatricians, it was simply with the thought of keeping them in touch with a new suggestion as to the etiology of RLF, and with no uncanny foresight of what has since happened. It is of interest that when Szewczyk's report was first submitted to the ophthalmological journal in which it was published, the claim was so startling that one of the leading ophthalmologists in the country spent hours going over the work and examining the infants. He reached the conclusion that there was "something in it, although just what he was uncertain" and recommended the acceptance of the report for publication. It was from a number of discussions with the ophthalmologist that the Editor became interested, as the conclusion was inevitable that if oxygen was an etiological factor the pediatricians quite unwittingly were, to a large extent, responsible for the disease, and were more involved in the situation than the ophthalmologist.